The association between nutritional status and outcomes after stroke

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King's College London

The association between nutritional status and outcomes after stroke

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A thesis submitted to King's College London for the degree of Doctor of Philosophy

Diabetes and Nutritional Sciences Division
School of Medicine - King's College London
2014

Publications

- **Paper**

Gomes F, Hookway C, Weekes C.E. 2014. Royal College of Physicians Intercollegiate Stroke Working Party evidence-based guidelines for the nutritional support of patients who have had a stroke. *Journal of Human Nutrition and Dietetics*, 27, 107-121.

- **Abstracts** (see appendices of published abstracts – A to J)

A – Gomes, F., Emery, P. W., Weekes, C. E. 2014. Abstract 63: Risk Of Malnutrition On Admission Predicts Mortality, Length Of Hospital Stay And Hospitalisation Costs At 6 Months Post Stroke. *Stroke*, 45:A63.
Oral communication delivered at the International Stroke Conference (San Diego, 2014)

B - Gomes, F., Emery, P. W., Weekes, C. E. 2014. Abstract T P142: Mortality And Stroke Recurrence In Obese Stroke Patients: The Obesity Paradox In a London-Based Population. *Stroke*, 45:ATP142.
Poster presented at the International Stroke Conference (San Diego, 2014)

C - Gomes, F., Emery, P. W., Weekes, C. E. 2013. Weight loss prior to stroke is associated with increased mortality and length of hospital stay at 6 months post-stroke. *International Journal of Stroke*. 8(Suppl 3):39.
Poster presented at the UK Stroke Forum Conference 2013 (Harrogate, 2013)

D - Gomes, F., Emery, P. W., Weekes, C. E. 2013. Risk of malnutrition, Body Mass Index and Waist Circumference as predictors of mortality after stroke. *Cerebrovascular Diseases*, 35(Suppl. 3):312
Poster presentation at the 22nd European Stroke Conference (London, 2013)

E - Aubrey, V. C., Gomes, F., Weekes, C. E. 2013. Nutrition screening tools can predict outcomes at one month in patients who have had a stroke. *Cerebrovascular Diseases*; 35(Suppl. 3):171.
Oral communication at the 22nd European Stroke Conference (London, 2013)

F - Aubrey, V. C., Gomes, F., Weekes, C. E. 2013. Concurrent validity of two nutrition screening tools in acute stroke patients. *Cerebrovascular Diseases.* 35(Suppl. 3):705.
Poster presentation at the 22nd European Stroke Conference (London, 2013)

G - Gomes, F., Hookway, C., Emery, P. W., Weekes, C. E. 2012. A systematic review of the evidence for oral nutritional supplements in patients at risk of malnutrition who have had a stroke. *Cerebrovascular Diseases*, 33(Suppl.2):1-2.
Oral communication at the 21st European Stroke Conference (Lisbon, 2012)

H - Gomes, F., Feeney, A., Prior, R., Weekes, C. E., Emery, P. W. 2012 Predictive validity of a nutrition screening tool: clinical outcomes at one year. *Age and Ageing*. 41 (suppl 1):43-43.
Poster presentation at the British Geriatrics Society Autumn Meeting (Brighton, 2011)

I - Gomes, F., Crichton, S., Wolfe, C., Emery, P. W., Weekes, C. E. 2011. Association between BMI and mortality after first-ever ischaemic stroke. *Cerebrovascular Diseases*, 31(suppl 2):1–322.
Poster presentation at the 20th European Stroke Conference (Hamburg, 2011)

J - Gomes, F., Feeney, A., Prior, R., Weekes, C. E., Emery, P. W. 2011. Predictive validity of the Nutrition Screening Tool currently used in St. Thomas Hospital. *Sinapse*, 11(1):106-107.
Poster presentation at the 5th Portuguese Stroke Conference (Porto, 2011)

Abstract

This thesis aimed to study the association between nutritional status (both undernutrition and overnutrition) and the post-stroke outcomes.

In the first study, the predictive validity of a nutrition screening tool was evaluated on hospitalised elderly and stroke patients. Patients identified as being nutritionally-at-risk had a significantly increased rate of mortality and a tendency for a longer length of hospital stay, when compared to adequately nourished patients.

In a second study, the association between Body Mass Index (BMI) and mortality after a first-ever stroke was explored, using data provided by the South London Stroke Register (which covers a multiethnic population of 234,533 inhabitants in South London). After adjusting for possible confounders and having the normal weight category as reference group, the risk of mortality (up to 8 years) was higher for the underweight and lower for the overweight category.

In the third study, the relationship between BMI, central obesity, nutrition risk categories and outcomes at 6 months post stroke was prospectively analysed. 550 patients were recruited on admission after stroke to two London-based hospitals. The higher the BMI, and the waist circumference (WC) quartile, the lower the rate of mortality, and there were no significant associations between BMI and WC with stroke recurrence. Patients at high risk of malnutrition had significantly higher risk of mortality, length of hospital stay and hospitalisation costs. Further research is needed to determine whether nutritional support (and which type) improves patients' outcomes.

A systematic review entitled "Oral nutritional supplements (ONS) in patients at risk of malnutrition who have had a stroke" was also conducted (as part of a review of clinical guidelines on stroke care) and it was concluded that there is a lack of good quality evidence supporting the role of ONS in the management of patients at risk of malnutrition following acute stroke.

Author’s contribution

For the first study (chapter 2), Ms. Rebecca Prior (temporary research dietitian) and Ms. Aoife Feeney (MSc student) were responsible for patient recruitment and baseline data collection (patient characteristics and the result of the nutrition screening tool). I was responsible for collecting the outcome data from computerised medical records for each recruited patient (at 4 different time-points) as well as its analyses.

For the second study (chapter 3), I was responsible for searching and selecting the potentially useful information that could be obtained from the South London Stroke Register, designing the study, obtaining approval, cleaning and organizing the database, analysing and interpreting the data.

For the third study (chapter 4), I was responsible for planning, designing, obtaining ethical and R&D approvals, recruiting and obtaining patients’ consent (or assent from their next of kin), collecting baseline data (demographic, clinical, anthropometric), obtaining approval and access to the outcome data from the National Episode Statistics, setting-up the database, analysing and interpreting the data.

I statistically analysed and interpreted the data for all the studies and composed the present thesis. All statistical analyses were conducted in discussion with my supervisors, Prof. Peter Emery, Dr Elizabeth Weekes, and two statisticians, Mr. Peter Milligan and Ms. Siobhan Crichton, who provided me with a very helpful advice.

I am extremely grateful for my supervisors’ guidance on all the phases mentioned above.

While doing my PhD, I also collaborated in the process to develop the 4th edition of the “National clinical guidelines for stroke”, created by the Royal College of Physicians Intercollegiate Stroke Working Party. I was responsible for conducting searches for 16 systematic reviews (in 5 databases) on nutritional support after stroke and secondary prevention, and I also evaluated the quality of relevant papers, by completing study eligibility forms, data extraction forms and evidence tables.

Acknowledgments

In my previous professional experience as a dietitian, I was the only nutrition professional in the multidisciplinary team of the small hospital where I was working. Among other tasks, it was my responsibility to ensure the nutritional management of stroke patients. The lack of common practices between units and countries (that I had observed), the gaps in the evidence about nutritional management and the relationship between malnutrition and outcomes after stroke drew my attention to these problems and increased my need to find experts and facilities that could support research in this area. That goal was achieved.

Professor Peter Emery and Dr Elizabeth Weekes, I am extremely grateful for your endless support, for sharing your extensive knowledge and for believing in me, since my very first steps in a new country, with a new language and health system. The guidance provided by both my supervisors, 2 statisticians (Mr. Peter Milligan, and Ms. Siobhan Crichton) and 2 experts in healthcare management (Prof. Simon Jones and Dr. Graham Cookson) was crucial for my (statistical) data analyses and for enabling me to understand the "Hospital Episode Statistics" encrypted data.

I also want to thank the teams of both Departments of Nutrition and Dietetics and both Stroke Units of St. Thomas' Hospital and Princes Royal University Hospital. They made me feel part of their teams and contributed to a fruitful and pleasant (long) journey. A special thank you to Alex Lang, for all the time he dedicated to help me. Patients and their relatives/carers, many of whom were severely ill and devastated, not only made the main study of my PhD feasible, but they also left me with really good memories; they were frequently contributing to my continuous and strong determination.

Thank you to Dr. Christine Baldwin and Information Specialists from KCL, for teaching me how a systematic search should be conducted in different databases.

I am also thankful to Ms. Siobhan Crichton and Professor Charles Wolfe for giving me authorisation to access the South London Stroke Register data (chapter 3), and thank you to Aoife Feeny and Rebbeca Prior for permission to access the baseline data of the patients who were included in the analysis of the first study (chapter 2).

It is a great privilege to be funded by the Portuguese Foundation for Science and Technology, which enables me to pursue this PhD program.

And, finally, my caring and supportive family, wonderful office mates and friends were equally important to help me through this experience. A special thank you should go to Bruno Serdoura, because of his Excel expertise, encouragement and incredible patience.

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Abbreviations

BAPEN – British Association of Parenteral and Enteral Nutrition

BMI – Body Mass Index

CHD - Coronary Heart Disease

GSTT – Guy´s and St Thomas´ NHS Foundation Trust

GSTT NST - Guy´s and St Thomas´ NHS Foundation Trust Nutrition Screening Tool

HASU – Hyper-acute Stroke Unit

HES - Hospital Episode Statistics

HRG - Healthcare Resource Groups

LOS - Length of hospital stay

MTD - Modified Texture Diets

NHS - National Health Service

NIHSS - National Institutes of Health Stroke Scale

NST – Nutritional Screening Tool

ONS - Oral nutritional supplements

ROC - receiver operating characteristic

SLSR - South London Stroke Register

STH – St Thomas' Hospital

SU – Stroke Unit

TIA - Transient Ischaemic Attack

WC – Waist Circumference

WHO – World Health Organisation

Chapter 1:

General introduction

1.1– Malnutrition

1.1.1– Definition

Malnutrition can be defined as a “state of nutrition in which a deficiency or excess (or imbalance) of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome” (Elia, 2000).

In other words, malnutrition relates to all deviations from adequate nutritional status, which includes energy undernutrition and overnutrition (obesity is a form of malnutrition) (Shetty, 2003). Overnutrition implies a positive nutrient balance and undernutrition a negative nutrient balance (Meijers et al., 2010).

Malnutrition arises from deficiencies of specific nutrients; for example, anaemia and xerophthalmia are symptoms of malnutrition caused by inadequate intake of iron and vitamin A.

The term “undernutrition” is used to refer to generally poor nutritional status, but also implies underfeeding. It is caused primarily by an insufficient energy intake, regardless of whether any other specific nutrient is a limiting factor (Shetty, 2003).

For the purposes of this thesis, undernutrition will be defined as malnutrition and overnutrition will be defined as obesity and/or overweight, as usually referred in the literature.

1.1.2 – Malnutrition (as undernutrition)

The World Health Organisation (WHO) defines nutrition as “the intake of food considered in relation to the body’s dietary needs”, affirming that good nutrition is a cornerstone of good health, and that poor nutrition can cause “reduced immunity, increased susceptibility to disease, impaired physical and mental development, and reduced productivity” (WHO, 2010).

Malnutrition in the general population

Malnutrition is both a cause and consequence of disease in adults and children (Brotherton et al., 2010) and, according to a national report, it is an under-recognized and under-treated problem that affects over 3 million people in the UK. The majority of these (93%) live in the community, with 5% in care homes and 2% in hospital (Elia and Russell, 2009).

One of the first experimental studies exploring the effects of malnutrition in healthy adult volunteers was conducted in 1944-1945. This study, known as the "The Minnesota Starvation Experiment", aimed to understand the physical and psychological effects of semistarvation and the problem of refeeding civilians who had been starved during the World War II. During the experiment, 36 male participants were subjected to semistarvation (approximately 1800Kcal/day during 6 months) in which most lost >25% of their weight, and many experienced anaemia, fatigue, apathy, extreme weakness, muscle soreness, hair loss, irritability, neurological deficits, lower extremity edema, decreased tolerance to cold temperatures and loss of sex drive (Kalm and Semba, 2005).

Weight is an indicator of nutritional status, hence the use of BMI as an indicator of chronic protein energy status. In general, a positive energy balance will result in weight gain and a negative energy balance will result in weight loss, with depletion of both body fat and muscle. Protein-energy deficiency is likely to be associated with micronutrient (vitamins, minerals and trace elements) deficiencies, although these can also occur in individuals with acceptable protein-energy status (e.g. a normal weight or overweight individual can have vitamin D or iron deficiency). Over time, nutrient deficiencies (macro and/or micronutrient) have a negative impact in multiple functions of the body (Stratton et al., 2003).
In different groups of population, malnutrition has diverse clinical effects and its associated consequences, as shown in the next table.

Table 1.1 - Clinical effects of malnutrition in the general population - reproduced from BAPEN (Brotherton et al., 2010)

Effect	Consequence
Impaired immune response	Impaired ability to fight infection
Reduced muscle strength and fatigue	Inactivity and reduced ability to work, shop, cook and self-care. Poor muscle function may result in falls, and in the case of poor respiratory muscle function result in poor cough pressure – delaying expectoration and recovery from chest infection
Inactivity	In bed-bound patients, this may result in pressure ulcers and venous blood clots, which can break loose and embolise
Loss of temperature regulation	Hypothermia with consequent further loss of muscle strength
Impaired wound healing	Increased wound-related complications, such as infections and un-united fractures
Impaired ability to regulate salt and fluid	Predisposes to over-hydration, or dehydration
Impaired ability to regulate periods	Impaired reproductive function
Impaired fetal and infant programming	Malnutrition during pregnancy predisposes to common chronic diseases, such as cardiovascular disease, stroke and diabetes (in adulthood)
Specific nutrient deficiencies	Anaemia and other consequences of iron, vitamin and trace element deficiency
Impaired psycho-social function	Even when uncomplicated by disease, malnutrition causes apathy, depression, introversion, self-neglect, hypochondriasis, loss of libido and deterioration in social interactions (including mother-child bonding)
Additional effects on children and adolescents	Growth failure and stunting, delayed sexual development, reduced muscle mass and strength, impaired neuro-cognitive development, rickets and increased lifetime osteoporosis risk

Although malnutrition affects several different populations/ages, this thesis will only focus on disease-related malnutrition, particularly in stroke and elderly patients.

Disease-related malnutrition: identification and consequences

The concerns regarding prevalence and adverse effects of disease-related malnutrition (malnutrition triggered by illness or disease) and in hospitalised patients were first reported more than 30 years ago (McWhirter and Pennington, 1994, Hill et al., 1977, Bistrian et al., 1976), justifying the need to correctly and promptly identify this unrecognised problem. The identification of malnutrition has been typically based on anthropometric, biochemical and physical parameters, among others. However, currently there is no universally accepted gold standard (best method) for the assessment of nutritional status (Donini et al., 2007, Foley et al., 2009b).

It was necessary to find a systematic and standardized approach to identify this condition, and that is where Nutritional Screening Tools (NST) have an important role (Bauer et al., 2010).

A NST helps to identify patients who are currently malnourished or at risk of becoming malnourished, so they can be referred for further assessment and nutritional intervention, if appropriate (Weekes et al., 2004). Ideally, NSTs should be accompanied by an action plan detailing appropriate monitoring procedures for low risk patients and clear guidelines for action e.g. food record charts or dietetic referral for high risk patients (Elia, 2000).

Nutrition screening and nutritional assessment are terms that are often used interchangeably and it is worth explaining how they differ.

Both techniques are usually presented as a questionnaire containing variables associated with malnutrition, and the responses to the questions are used to determine the individual's nutritional status or risk of malnutrition (Jones, 2006).

Nutrition screening is the first step in determining nutritional problems. Screening should rapidly and accurately identify individuals who should be referred to the nutrition specialist (e.g. dietitian, expert clinician) for a further assessment, where it would be possible to gather more information and determine if there truly is a nutrition problem, to understand the cause of the problem and to determine its severity.

In general, nutritional assessment continues the data gathering process initiated in the screen. The types of data collected in nutritional assessment are often similar to data collected in the screening process but in more depth. For example, whereas the screen simply determines whether there have been changes in intake, the assessment determines the amount of change and the nutrients impacted (Charney, 2008).
Other examples are presented in the following table, reproduced from "*Nutrition screening vs. nutrition assessment: how do they differ?*" (Charney, 2008).

Table 1.2 - Level of detail of the nutrition screen compared with nutritional assessment (Charney, 2008)

Parameters	**Nutrition Screen**	**Nutrition Assessment**
Intake	Recent changes in intake (time period)	Changes in specific nutrient intake Changes in energy intake Changes in texture Impact of changes
Anthropometrics	Weight Change in weight (time period) Height	Body mass index Body composition
Medical tests, laboratory tests, and procedures	Not usually included	Medical diagnosis Impact of medical diagnosis on ability to meet needs
Nutrition-focused physical exam	General appearance	Review of systems Physical examination
Patient history	Not usually included	Medical and surgical history Planned therapies Medication history Social history

According to a review carried out in 2008, the prevalence of hospital malnutrition in 20 studies conducted in various countries and several groups of diseases after 1990 was reported to range between 20% and 50% (Norman et al., 2008). This wide range may be partially explained by the different criteria used to diagnose malnutrition.

Evidence suggests that malnutrition in association with illness is an independent predictor of mortality, and these findings apply to heterogeneous populations, including young and old hospitalised patients with a wide range of diseases (Landi et al., 2000, Gariballa and Forster, 2007).

Due to impaired immune function, a state of malnutrition has been reported to increase the susceptibility to adverse clinical outcomes such as postoperative complications (Campos and Meguid, 1992), infections, gastrointestinal haemorrhages and pressure sores (Dennis, 2003, Chandra, 1979).

Cognitive impairment (Correa Leite et al., 2001) and decreased muscle function with impaired functional status (Norman et al., 2008) are also associated with poor nutritional status. As a result of all these consequences, quality of life can be compromised by a state of malnutrition (Vetta et al., 1999).

Due to an increased morbidity, malnourished patients experience a significantly prolonged treatment duration and length of hospital stay (LOS). The average LOS in 9 studies, conducted in different countries, was increased by 40–70% in malnourished patients when compared with the adequately nourished (Norman et al., 2008).

Economic burden of disease-related malnutrition

Malnutrition poses a greater burden on healthcare resources since malnourished patients have more GP visits, more hospital admissions (with 65% and 82% more, respectively, for the elderly), longer LOS, and are also more likely to be admitted to care homes, when compared with well-nourished individuals (Elia, 2006).

Amaral et al. suggested that disease-related malnutrition is an important determinant of hospitalisation costs, being responsible for an increase in 20% of these costs (Amaral et al., 2007). In this study, conducted with 469 hospitalised patients with a wide range of diseases, those identified as being nutritionally at risk were more likely to be older, thinner, with lower functional capacity, and being transferred from or to

other hospitals. Also, the inpatient mortality (11% vs. 2%) and LOS (14.7 vs. 7.6 days) were significantly higher in this group, which contributes to the increased costs.
In the United States of America, hospital charges were estimated to be from 35% to 75% higher for malnourished patients than for well-nourished patients (Gallagher-Allred et al., 1996).
Public expenditure on disease-related malnutrition in the UK in 2007 has been estimated at in excess of £13 billion per annum, about 80% of which was in England (Elia and Russell, 2009). Despite these figures, there is a paucity of Department of Health data relating to the burden of malnutrition (Elia and Russell, 2009).

The impact of malnutrition may be significantly reduced if it is recognised early and treated with relatively simple measures. Effective screening for risk of malnutrition, nutritional care planning, delivery of high standards of food service and appropriate nutritional support are recommended in all settings (Brotherton et al., 2010).

Potential benefits of nutritional intervention

Given that malnourished patients are more likely to suffer negative outcomes, the aim of identifying nutritionally vulnerable patients is to implement nutritional interventions that might result in the improvement of these outcomes.
There are different types of nutritional interventions, such as dietary counseling, food fortification, oral nutritional supplements (ONS), enteral tube feeding (nasogastric or gastrostomy) and parenteral nutrition. These nutrition support interventions aim to meet all patients' needs regarding energy, protein, fluid and micronutrients (NICE, 2006a).
Evidence from systematic reviews and meta-analyses shows that these interventions, when used appropriately, result in a number of benefits. Stratton and her colleagues concluded that ONS can significantly improve clinical outcome (mortality, complication rates and reduced LOS) in certain patient groups at risk of malnutrition

(particularly in the hospital setting), which may be due to increase in energy and nutrient intake, body weight and muscle mass. Similar conclusions were drawn while assessing the effect of enteral tube feeding alone or the combined effect of ONS and enteral tube feeding (Stratton et al., 2003, Stratton and Elia, 2007). These authors had the ambitious aim of establishing an evidence base for nutritional interventions in different groups of patients and, therefore, reviewed several trials with a wide range of interventions, outcomes, conditions and settings, which makes it difficult to present a summary of all their analyses and results. For example, one of the aims was to analyse the effect of enteral tube feeding (as a sole source of nutrition, as a supplement to food intake or in combination with parenteral nutrition) on clinical outcomes of patients in hospital (Stratton et al., 2003). Several electronic databases were searched and 74 trials of enteral tube feeding in the hospital setting were reviewed, which included randomised and non randomised trials. Randomised controlled trials (n=33) were assessed with the Jadad scoring system, and the majority had low Jadad scores (i.e. had poor study designs). When the outcome was restricted to mortality, 12 trials (n= 600 patients) had information available on mortality rates in patients with a number of conditions: burns, critical illness/injury, gastrointestinal/liver diseases, cancer, orthopaedics and surgery. Pooled analysis of the effects of enteral tube feeding (vs. routine clinical care or no nutritional support) showed a significantly reduced risk of mortality (OR 0.48, 95% CI 0.30-0.78) with no significant heterogeneity between studies. These positive results should, however, be interpreted with caution because of the poor quality and small sample sizes of the studies included and their clinical heterogeneity (attributable to a variety of underlying conditions).

While it seems that the beneficial effects of nutritional support are observed when the analyses combine studies conducted in patients with a variety of conditions, this may not be true for analyses that are condition-specific (e.g. cancer), where the beneficial effects are shown to be very limited. For example, a meta-analysis of 13 studies demonstrated that oral nutritional interventions (compared with routine care) are effective at increasing weight and nutritional intake and improving some aspects of quality of life in patients with cancer who are malnourished or are at nutritional risk, but failed to show improvement in mortality (Baldwin et al., 2012). Baldwin and colleagues followed the methodology recommended by the Cochrane Collaboration. Searches were conducted to find randomised controlled trials or quasi-randomised controlled trials undertaken in malnourished or at risk of malnutrition adults with cancer at all sites and all stages; interventions included dietary advice, oral nutritional supplements and outcome measures included mortality and quality of life (primary outcomes) and weight change and energy intake (secondary outcomes). Subgroup analyses were also carried out. The quality of the 13 included studies was clearly described and considered to be from low to moderate, and all trials were considered to be at risk of bias (e.g. only 1 study reported blinded assessment of some outcomes). Risk of mortality between the intervention and control groups was 1.06 (95% CI 0.92-1.22, with no significant heterogeneity) in 11 studies, with a length that varied from 6 weeks to 36 months.

5 studies collected quality of life data from the same cancer-specific questionnaire, but they reported results in different components of quality of life. The first analysis revealed statistically significant improvements in the majority of the components with high heterogeneity; thus, further analyses removed the studies that accounted for heterogeneity and showed that interventions resulted in statistically significant improvements of 4 components: emotional function, global quality of life, dyspnea and loss of appetite. Regarding the effect on nutritional status (data on body weight from 8 studies and on energy intake from 4 studies), intervention (vs. routine care) was associated with a statistically significant weight gain (mean difference in weight = 1.86 kg, 95% CI 0.25-3.47, with significant heterogeneity, I^2=76%) and increase in energy intake (mean difference in energy intake = 432 kcal/d, 95% CI 172-693, with significant heterogeneity I^2=97%). However, these results were no longer significant after removing the main sources of heterogeneity.

In addition, a Cochrane review examined trials for improvement in nutritional status and clinical outcomes (weight change, dietary intake, mortality, morbidity, functional status, among others) when oral protein and energy supplementation was provided to elderly people (Milne et al., 2009). Using 6 electronic databases and a hand search, authors searched for randomised and quasi-randomised controlled trials of study groups with a minimum average age of 65 years, except groups in critical care or recovering from cancer treatment. Interventions included commercial sip feeds, milk based supplements and fortification of normal food sources, compared with usual practice or placebo, for a minimum period of 2 weeks. Further analyses were conducted in subgroups of individuals who were undernourished, who were ill, those aged 75 years or over, those who received supplements of 400Kcal or more, and those who had a longer duration of supplementation (35 days or more). Data extraction and

quality assessment of included studies (using a protocol that scores 10 items) was carried out by 2 reviewers.
Heterogeneity was assessed and, when significant (>50%), a random effects model was applied. Sensitivity analyses were conducted to assess the influence of study quality, of large studies and of studies sponsored by the industry on effect size.
62 studies with 10187 participants from Europe, USA, Canada, Australia and Hong King, were included. 48% of the individuals had no specified disease or condition, but other studies included a wide range of diseases or conditions (e.g. stroke, congestive heart failure, hip fracture), and 60% of all participants were screened for risk of malnutrition, although the method varied between studies (therefore, there was no standard methodology to assess nutrition risk). The type and length of intervention received also varied between studies, e.g. additional energy varied from 175 to 1350Kcal/day and protein from 10 to 50g/day, some trials provided extra vitamins and minerals, and the intervention period (as well as follow-up period) varied from 10 days to 18 months.
Supplementation produced a small but consistent weight gain in older people and mortality was reduced by supplementation in older people who were undernourished. In other words, the pooled weighted mean difference for percentage weight change (which was measured in 42 trials with 3058 participants) in intervention vs. control was 2.2% (1.8 – 2.5) with no significant heterogeneity. Risk of mortality by the end of the follow-up period for all participants of studies that assessed mortality (n=8031) was not significantly reduced for the intervention group vs. control (RR 0.92, 95% CI 0.81-1.04), but was significantly reduced when analyses were restricted to studies in which participants (n=2461) were defined as undernourished (RR 0.79, 95% CI 0.64-0.97). When analyses were limited to higher quality studies with concealed randomisation (n=15 studies, 6604 participants), results were consistent (RR 0.91, 95% CI 0.79-1.03), and supplementation was beneficial with statistical significance (RR 0.78, 95% CI 0.62-0.98) when limited to patients with a variety of geriatric conditions (most of them hospitalised, n=2701).
There may also be a beneficial effect of supplementation on complications (such as infective complications and pressure sores) as, in 24 trials, RR of complications was 0.86 (95% 0.75-0.99) with no statistically significant heterogeneity, but no evidence was found of improvement in functional benefit or reduction in LOS with ONS. However, the authors noted that most studies had an intervention time that was too

short to have a realistic chance of causing differences in morbidity, functional status or quality of life. It should be noted that the quality of the majority of the included studies was poor, particularly regarding blinding (of outcome assessors, participants and treatment providers) and other possible sources of biases include inadequate reporting of numbers of participants who were allocated and assessed, and reasons for losses to follow-up. Compliance with supplements may be a problem and a limitation in studies using supplements and, for those trials that measured it, some of them reported problems with acceptance or adverse effects. The symmetrical funnel plot for the outcome mortality suggested no evidence of publication bias but the Egger test was not conducted.

1.1.3 – Obesity (as overnutrition)

Definition

Obesity is a multifactorial chronic disease characterized by an excess of fat in the body that has significant health consequences. However, the amount of excess fat, its distribution within the body, and the associated health consequences vary considerably between individuals with obesity (World Health Organization, 2000).
Although it affects a wide age range, this thesis will only focus on obesity in adult life.

The prevalence of overweight and obesity is commonly assessed by using body mass index (BMI), defined as the weight in kilograms divided by the square of the height in metres (kg/m^2). The WHO defines overweight as a BMI between 25 to 29.9 kg/m^2 and obesity as a BMI over 30 kg /m^2. Additionally, different classes of obesity are defined: class I, BMI 30 - 35 kg /m^2; class II, BMI 35 - 40 kg /m^2; class III, BMI greater than 40 kg /m^2. The risk of comorbidities associated with obesity is continuous and graded and the classification was based on observational and epidemiological studies which relate BMI to risk of morbidity and mortality. Normal weight is classified as a BMI between 18.5 to 24.9 kg/m^2 and a BMI less than 18.5 kg/m^2 is considered underweight.

BMI does not measure body fat mass and may not correspond to the same degree of fatness or associated health risk in different individuals and populations; however, it allows meaningful comparisons between them and a firm basis for evaluating interventions (World Health Organization, 2000).

The adipocyte (adipose cell) is not only a store of lipids that can be used to meet future needs of the body, it also works as an endocrine cell, being able to communicate with the brain in the regulation of various body functions. It is through the production of proteins with a prothrombotic action, such as plasminogen activator inhibitor-1, and inflammatory cytokines, such as TNF- α, interleukin-6, angiotensinogen, adiponectin and others, that the adipose tissue participates in mechanisms thatcan lead to hypertension, type 2 diabetes mellitus and cardiovascular diseases (Flier, 2004).

Adipose tissue (composed of adipocytes, inflammatory cells, etc.) is distributed throughout the body, being approximately 85% located under the skin (subcutaneous adipose tissue) and 15% located within the abdomen (intra-abdominal adipose tissue) (Klein et al., 2007).

Compared with subcutaneous adipose tissue, visceral (intra-abdominal) adipose tissue has more cells per unit mass, higher blood flow, more glucocorticoid (cortisol) receptors, probably more androgen (testosterone) receptors, and great cathecolamine-induced lipolysis, which makes this tissue more susceptible to both hormonal stimulation and changes in lipid accumulation and metabolism (World Health Organization, 2000).

The type of distribution of fat has different associated risks. Abdominal obesity (also called android obesity, or central obesity or upper body obesity) is related with an increased risk of metabolic complications (such as insulin resistance and raised blood pressure), while gynoid obesity - characterised by an more evenly and peripheral distribution of fat around the body - is associated with a lower risk (World Health Organization, 2000).

The mechanisms that explain the association between excess intra-abdominal fat accumulation (abdominal obesity) and metabolic complications are unknown (Klein et al., 2007) but some hypotheses have been proposed. For example, the “lipid overflowectopic fat model" suggests that excess intra-abdominal fat accumulation may indicate that an individual's subcutaneous adipose tissue is unable to serve as an "energy sink" for an energy surplus (due to excess of energy intake and/or reduced energy expenditure). This inability of subcutaneous adipose tissue to store the excess energy (due to factors such as smoking, genetic susceptibility to abdominal obesity, etc.) would result in increased accumulation of fat at undesired locations, such as liver, heart, pancreatic β-cells - a phenomenon called ectopic fat distribution. The resulting metabolic consequences of this "defect" in energy partitioning include visceral obesity, insulin resistance, an atherogenic dyslipidaemia and a pro-thrombotic, inflammatory profile, which are defining features of metabolic syndrome (Despres and Lemieux, 2006).

The amount of abdominal fat can vary dramatically within a narrow range of total body fat and BMI, which explains the need of having additional measures to identify obesity and its risks (World Health Organization, 2000).

Waist circumference (WC), measured at the midpoint between the lower border of the rib cage and the iliac crest, is a convenient and simple method considered the best surrogate of visceral adiposity across a wide age range (Onat et al., 2004). WC provides a measure of fat distribution that cannot be obtained by measuring BMI (Klein et al., 2007).

An increased risk of metabolic complications is associated with a WC of 80 cm or greater in women and 94 or greater in men; a substantially increased risk is associated with a WC of 88 cm or greater in women and 102 or greater in men. However, it should be noted that populations differ in the level of risk associated with a particular WC (World Health Organization, 2000).

Health consequences and the economic burden of obesity

There are various health problems associated with obesity, with different relative risks (RR). Type 2 diabetes mellitus, gallbladder disease, dyslipidemia, insulin resistance and sleep apnoea are greatly increased in obese individuals (RR greater than 3). Obesity also moderately increases (RR 2-3) the risk for coronary heart disease (CHD), hypertension and osteoarthritis, and slightly increases (RR 1-2) the risk for certain cancers and reproductive hormone abnormalities. Moreover, abdominal obesity in particular is an independent predictor for type 2 diabetes mellitus, CHD, hypertension, breast cancer and premature death (World Health Organization, 2000).

Several benefits of intentional weight loss in these diseases have been described, including marked improvements in type 2 diabetes mellitus, dyslipidemia, hypertension, cardiovascular risk, ovarian function, breathlessness, sleep apnoea and osteoarthritis (World Health Organization, 2000). As an example, a meta-analysis of 25 randomised controlled trials involving 4874 participants with different ethnicities showed a significant reduction in systolic blood pressure of -4.4 mmHg and a significant reduction in diastolic blood pressure of -3.6 mmHg for an average weight reduction of 5Kg (Neter et al., 2003).

In England, the proportion of men classed as obese increased from 13% in 1993 to 24% in 2011 and from 16% to 26% for women during the same period. By 2025, it is estimated that 47% of men and 36% of women will be obese (NHS, 2013).

In 2007, estimates of the direct NHS costs of treating overweight and obesity, and related morbidity in England were £4.2 billion. The indirect costs estimates ranged between £2.6 billion and £15.8 billion (Morgan and Dent, 2010).

1.2 - Stroke

Definition

The WHO defines stroke as “a focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours (or leading to death), and of presumed vascular origin” (World Health Organization, 2006).
In other words, stroke is a disruption of blood supply to the brain, whether due to blood vessel occlusion (ischaemic stroke) or rupture with bleeding (haemorrhagic stroke). Cell function and survival is limited by lack of oxygen and nutrients, as the blood supply becomes compromised or is interrupted. A zone of cell death is created, bordered by a zone of damaged cells (Kidd, 2009).
The site and extent of this damage within the brain determines whether the stroke is fatal or causes permanent or temporary disabilities (Carroll et al., 2001). Although some strokes may not totally destroy vital areas of the brain, they can still cause ongoing impairment of motor, sensory, or processing pathways and an associated degradation of quality of life (Kidd, 2009).

Stroke is just one of a range of disorders affecting the arteries in the brain, collectively known as cerebrovascular diseases (Wolfe and Rudd, 2005); and these diseases are included on the group of disorders of the heart and blood vessels - the cardiovascular diseases - which are the number one cause of death globally (WHO, 2009).

Stroke subtypes and types of stroke events

There are two major stroke subtypes, as mentioned before: the ischaemic and the haemorrhagic stroke.
The ischaemic stroke accounts for approximately 85% of all strokes and is caused by a sudden obstruction in an artery supplying blood to the brain (Wolfe and Rudd, 2005). Its symptoms last at least 24 hours and may be caused by:
– a narrowing of the artery (atherosclerotic stroke)

– a blood clot forming in the artery (thrombotic stroke)
– a blood clot or other tissue fragment travelling to the brain from elsewhere in the body (embolic stroke).

The haemorrhagic stroke accounts for the remaining 15% of strokes and leads to a bleeding in the brain from a ruptured blood vessel (Wolfe and Rudd, 2005). In the same way, its symptoms last at least 24 hours, and the vessel may rupture because it is:

– weakened (e.g. by an aneurysm)
– abnormally formed (e.g. arteriovenous malformation)
– subjected to trauma (e.g. a head injury)

The bleeding may occur in the soft tissues of the brain - intracerebral haemorrhage – or in the space between the surface of the brain and the skull (i.e., between the two meninges, pia mater and arachnoidea) - subarachnoid haemorrhage (Wolfe and Rudd, 2005).

The reference used to provide these figures (Wolfe and Rudd, 2005) is a White Paper created by national stroke experts who use mainly worldwide data. Although there is no reference in this white paper related with the proportion of ischaemic and haemorrhagic strokes, it seems to be safe to assume that these are worldwide figures. Other authors (Markus et al., 2010) state that these are the figures for developed countries.

A transient ischaemic attack (TIA) differs from stroke only in degree (Kidd, 2009). TIAs are also caused by a blockage in the arteries supplying blood to the brain, or less frequently by small haemorrhages, but symptoms are temporary and typically last less than 2 hours, although the definition is up to 24 hours (Wolfe and Rudd, 2005).

In a WHO manual created for guidance on well-conducted stroke surveillance, (World Health Organization, 2006), the following divisions of types of stroke events are recommended:

- first ever stroke: referring to people who have never had a stroke before, and this excludes previous TIAs (as a TIA is not considered a stroke)
- recurrent stroke: referring to people with history of previous stroke

- non-fatal stroke: referring to people who survived at least 28 days after the onset of the stroke symptoms.
- fatal stroke: referring to people who died within 28 days of stroke symptom onset.

Symptoms and diagnosis

The brain is a highly complex organ and its different parts control different functions of the body. Thus, the consequences of stroke are wide-ranging because they depend on the region of the brain affected, as well as the nature and severity of the damage (Wolfe and Rudd, 2005).
The possible symptoms of a stroke are as follows (World Health Organization, 2006).

Table 1.3 – List with possible symptoms of a stroke, reproduced from "WHO STEPS Stroke Manual" (World Health Organization, 2006)

• Unilateral or bilateral motor impairment (including lack of coordination)

• Unilateral or bilateral sensory impairment

• Aphasia/dysphasia (non-fluent speech)

• Hemianopia (half-sided impairment of visual fields)

• Forced gaze (conjugate deviation)

• Apraxia of acute onset

• Ataxia of acute onset

• Perception deficit of acute onset

• Dizziness, vertigo

• Localized headache

• Blurred vision of both eyes

• Diplopia

• Dysarthria (slurred speech)

• Impaired cognitive function (including confusion)

• Impaired consciousness

• Seizures

• Dysphagia

The clinical impression of focal neurological deficits related to a specific vascular territory is usually followed by a diagnostic workup. This includes the differentiation between cerebral infarction and haemorrhage using neuroimaging techniques and a search for specific causes, such as embolism or large artery atherothrombosis (Curioni et al., 2009).

The neuroimaging techniques used for the diagnosis of a stroke include a computed tomography (CT), which is the most widely available diagnostic method for exclusion of alternative diagnoses and to rule out the presence of haemorrhage (that is a contraindication to the use of thrombolytic agents) and magnetic resonance imaging (MRI), which has excellent capacity to delineate the presence, size, location, and extent of hyperacute ischemia (Curioni et al., 2009, Kidwell et al., 2004).

The burden of stroke: incidence, mortality and costs

Every year, over 15 million people worldwide suffer a stroke, of which 5 million die and another 5 million are left significantly disabled (WHO, 2004).

Stroke carries a high risk of death, being the third most common cause of death in developed countries, exceeded only by coronary heart disease and cancer, as seen in figure 1.2, reproduced from “The Atlas of Heart Disease and Stroke” WHO document (WHO, 2004),

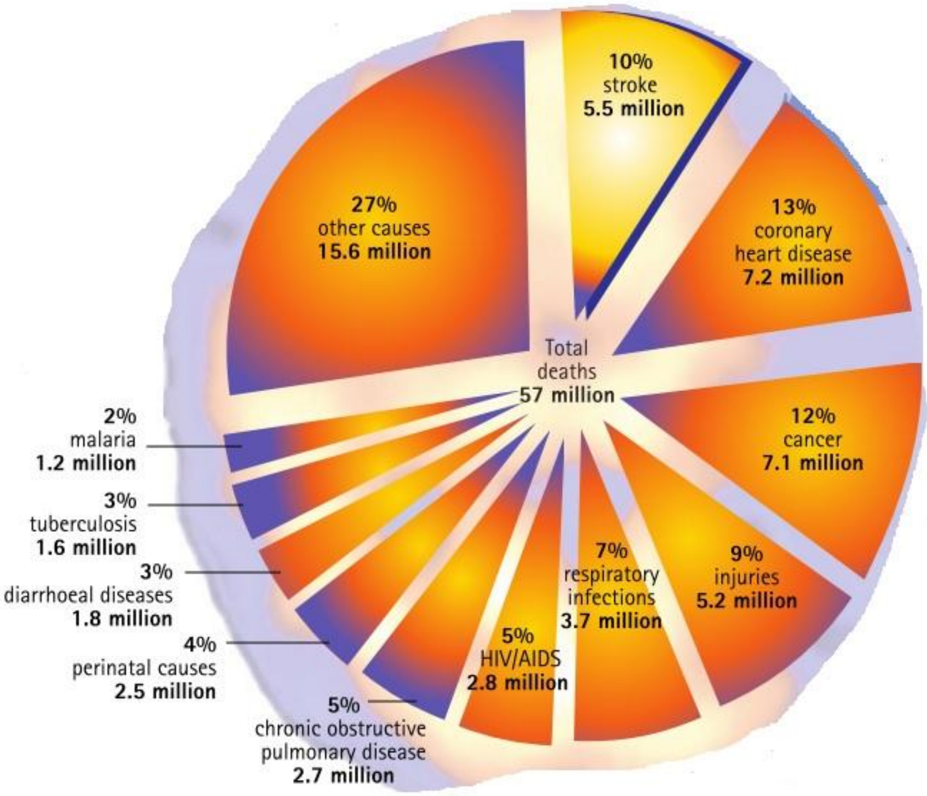


Fig. 1.1 – Percentages and number of deaths from stroke compared with other causes (WHO, 2004)

In England and Wales, stroke accounts for 11% of all deaths (RCP, 2012). In England, there are at least 110 000 new strokes per annum, nearly 1 million stroke survivors and over half are dependent on others for everyday activities (Markus et al., 2010). The cumulative risk of stroke recurrence is 26% within 5 years of a first stroke and 39% by 10 years (Mohan et al., 2011).

The incidence of stroke is declining in many westernized countries, largely as a result of reduction of levels of hypertension and smoking (in the stroke population), in conjunction with the introduction of statin and antiplatelet therapy for primary prevention (in those with vascular risk factors). However, the absolute number of strokes continues to increase because of the ageing population (WHO, 2004, Markus et al., 2010). For instance, in England the proportion of older people is predicted to rise from 16% in 2003 to 23% in 2031 (Markus et al., 2010). Some demographic factors, such as sex, age, race or ethnicity have been described to influence the incidence of stroke. Almost 1 in 4 men and nearly 1 in 5 women aged 45 years can expect to have a stroke if they live to their 85th year. Men have a 25-30% increased chance of having a stroke and the incidence doubles with each successive decade over the age of 55 years (Wolfe, 2000), having been estimated that 81% of strokes are in people more than 64 years old (Carroll et al., 2001). Additionally, African-Caribbean and African populations have approximately double the risk of stroke compared to the Caucasian population (Wolfe, 2000).

In the first year after a stroke about 30 % of patients will die, most within the first ten days (Carroll et al., 2001). The mortality rates are higher for intracerebral and subarachnoid haemorrhages than for ischaemic stroke, and higher in Caucasian than in African–Caribbean patients (Wolfe, 2000, Andersen et al., 2009).

Stroke is a costly disease because of the large numbers of premature deaths, ongoing disability in many survivors, impact on families/carers and impact on health services (World Health Organization, 2006). It should be noted that over one-quarter of strokes occur in people of working age (Markus et al., 2010). One measure of the burden of the disease is called disability-adjusted life years (DALYs), which is the combination of years of potential life lost due to premature death with years of productive life lost due to disability. The WHO predicts that DALYs lost to stroke will rise from 38 million in 1990 to 51 million in 2020 (WHO, 2004).

In 2009, an analysis on the cost of stroke in the United Kingdom from a social perspective concluded that the treatment of and productivity loss arising from stroke costs £8.9 billion a year, with treatment costs accounting for approximately 5% of total UK National Health Service (NHS) costs. Direct care accounted for approximately 50%, informal care costs 27% and indirect costs 24% (Saka et al., 2009). Besides the economic costs, e.g. the cost of healthcare and lost productivity, other costs are harder to calculate although equally important, e.g. the emotional cost of losing an important and valuable person through premature incapacity or death (Wolfe and Rudd, 2005).

Risk factors

Stroke is a multifactorial disease where a combination of risk factors influences the probability of suffering a stroke. The WHO considers the following major risk factors that can be divided into the 3 categories:

- modifiable:

  hypertension, smoking, physical inactivity, diet (low fruit and vegetable consumption), heavy alcohol consumption, overweight, diabetes (and atrial fibrillation and other cardiac diseases in developed countries)
- environmental:

  passive smoking, access to medical treatment.
- non-modifiable:

  age, sex, ethnicity, family history and genetic predisposition

The role of hypercholesteraemia as a risk factor for stroke was considered controversial, as there is evidence that lower total cholesterol levels might be associated with a decreased risk of ischaemic stroke but increased risk of haemorrhagic stroke (World Health Organization, 2006). This is supported by a study that found that higher total and lower high-density lipoprotein cholesterol levels are associated with increased risk of only ischaemic stroke (Tirschwell et al., 2004).
Other minor risk factors have been identified, which include drug use, migraine, oral contraceptive pill use, infections and thrombophilia (Markus et al., 2010).

Risk factors are reported to be different between ischaemic and haemorrhagic strokes (O'Donnell et al., 2010)), between first and recurrent strokes (Carroll et al., 2001), between very old (>80 years old) and younger stroke patients (Cristensen et al., 2010) and between different ethnic groups (Hajat et al., 2004).
For instance, in a study that analysed associations between stroke (first ever and recurrent) and its potential risk factors using national data, Carroll and his colleagues found that the strongest associations with first ever strokes were previous TIA, increasing age, atrial fibrillation, diabetes, heart failure, ischaemic heart disease, hypertension and smoking. For recurrent stroke, there were statistically significant associations with previous stroke, TIA, hypertension, increasing age and diabetes (Carroll et al., 2001).

It could be argued that stroke risk factors, among other factors (such as stroke subtype and severity of stroke), may confound the relationship between nutritional status and mortality. Thus, later in this thesis (chapter 3 and 4), the variables presented in the following table were considered to be potential confounders and/or effect modifiers and treated as such in the multivariable models.

Table 1.4. - Potential confounders, effect modifiers and the direction of the association between these parameters with the exposure (indicators of nutritional status such as BMI and risk of malnutrition) and the outcome (mortality)

Potential confounders and effect modifiers	Direction of association	Reference(s)
Age	- obese stroke patients tend to be younger (than non-obese), and the association between BMI and mortality may be different in different groups of age - age is positively associated with undernutrition	(Towfighi and Ovbiagele, 2009) (Yoo et al., 2008)
Gender	- among stroke survivors, women are more likely to have a higher BMI - women have strokes later in life; stroke mortality rate is higher in men among those younger than 65 years but higher in women among patients aged 75 years or older	(Towfighi and Ovbiagele, 2009) (Haast et al., 2012)
Ethnicity	- black stroke patients have higher rates of obesity and white stroke patients have a higher risk of mortality	(Markus et al., 2007) (Wolfe et al., 2005)
Type of stroke **Severity of stroke (NIHSS score)**	- the type and severity stroke are strongly linked to mortality, e.g. haemorrhagic strokes tend to be more severe and associated with increased mortality - nutritional status may be associated with type of	(Andersen et al., 2009) (Choi-Kwon et al., 1998) (Ryu et al., 2011)

	stroke and severity of stroke e.g. malnutrition (including low BMI) is more prevalent in haemorrhagic strokes and is associated with higher NIHSS scores	(Yoo et al., 2008)
Stroke risk factors * - hypertension, - diabetes, - dyslipidemia, - smoking, - IHD, - heart failure, - atrial fibrillation, - previous TIA - heavy alcohol consumption	- high total and lower HDL cholesterol increases risk of ischemic stroke - heavy alcohol consumption increases risk of total stroke (stronger association with haemorrhagic stroke) - all other risk factors increase the risk of total stroke - the majority of the risk factors are positively associated with BMI and have a similar effect (i.e. increased risk) on stroke incidence as on stroke mortality	(Tirschwell et al., 2004) (O'Donnell et al., 2010) (Carroll et al., 2001, Andersen et al., 2009) (Hart et al., 2000)

*These stroke risk factors were slightly different between chapter 3 (hypertension, CCF, angina, myocardial infarction, TIA, migraine, atrial fibrillation, diabetes, depression, hypercholesterolaemia) and chapter 4 (hypertension, diabetes, dyslipidemia, smoking, IHD, heart failure, atrial fibrillation, previous TIA and heavy alcohol consumption) – selected by myself, before collecting the data. In chapter 3, I had to use the risk factors that were available in the SLSR database and that were provided to me. In Chapter 4, these risk factors were selected by myself, while designing the study, and were based on studies that determined the risk factors for first and recurrent strokes, as well as ischaemic and haemorrhagic strokes.

1.3 – Malnutrition and stroke

The prevalence of malnutrition among stroke patients and its consequences has been studied by several authors.

When nutritional status is assessed in the acute stage after stroke, i.e. within a few days after hospital admission, prevalence of malnutrition has been reported to be between 9 and 62% (Axelsson et al., 1988, Dennis, 2003, Yoo et al., 2008, Westergren et al., 2001a, Choi-Kwon et al., 1998, Davalos et al., 1996) . Some studies have observed that the nutritional status of a significant proportion of patients deteriorates during hospital stay (Axelsson et al., 1988, Yoo et al., 2008, Mosselman et al., 2013, Davalos et al., 1996) and others have reported a high prevalence of malnutrition (affecting half of participants) at admission to rehabilitation services, with a mean of 22 days after stroke (Finestone et al., 1995).

Compared with the adequately nourished, malnourished stroke patients are more likely to have an increased mortality and morbidity, including poor clinical outcomes (development of more infections and pressure sores), functional outcomes (with a higher dependency, lower mobility and capacity for self care) and longer length of hospitalisation, among others. Some of the studies supporting these findings will be discussed below.

An international multicenter randomized trial “Feed Or Ordinary Diet” trial (FOOD trial) was conducted to evaluate various feeding policies on stroke patients (Dennis et al., 2006). A total of 5033 participants were enrolled between 1995 and 2003, and an observational study was conducted with the first 3012 patients to determine whether baseline nutritional status (mainly based on “bedside assessment”) was an independent predictor of 6-month outcome after stroke. Of the 275 (9%) undernourished patients, 37% were dead by final follow-up compared with only 20% of patients with “normal nutritional status”. This relationship was maintained after adjustment for age, pre-stroke functional state, and stroke severity. Undernourished patients had statistically significant higher rates of pneumonia, other infections, pressure sores and gastrointestinal haemorrhages during their hospital admission, when compared with those classified as “normal” and “overweight” (Dennis, 2003).

Similar findings were obtained by Davalos et al in 1996, in a study that included 104 patients admitted to hospital within 24h post stroke. Their nutritional status was assessed on admission and after 1 week: 16% were considered to be malnourished on admission and 26% at 1 week, as defined by a serum albumin less than 35g/L or a triceps skinfold thickness or the mid-arm muscle circumference less than the 10^{th} percentile of their reference population. When compared to patients with normal nutritional parameters, malnourished patients (after the first week of hospitalisation) had significantly higher levels of urinary cortisol (increased stress reaction, $p=0.025$), higher frequency of respiratory or urinary infections (50% vs. 24%, $p=0.017$) and bedsores (17% vs. 4%; $p=0.054$), increased number of deaths at 1 week (5 vs. 1 patient, $p=0.005$), poor functional capacity at 1 month (Barthel Index ≤ 50: 70.8% vs. 35.8%, $p=0.012$) and a longer duration of hospitalisation (median of 28 days vs. 17 days, $p=0.001$) (Davalos et al., 1996). However, when severity of stroke and swallowing disability at admission were included in the logistic regression model, malnutrition was not selected as an independent predictor of poor prognosis (death or Barthel Index ≤ 50 at 1 month). This may be partly explained by the criteria used to define malnutrition (as explained below, in the next page, albumin is not a good indicator of nutritional status in periods of acute illness), by the relatively small sample size or the relatively short follow-up period. Thus, stroke severity and swallowing disability seem to be important determinants of poor prognosis and any future study will need to take these into account and will need to be large enough to test whether there is an effect of malnutrition that is independent of these factors.

Gariballa et al aimed to measure the effect of nutritional status in 201 hospitalized stroke patients on clinical outcome, using a variety of anthropometric and biochemical parameters. After adjusting for age, comorbid conditions, sex, medications and stroke severity, serum albumin (that was used as an indicator of nutritional status) was related to mortality at 3 months after admission. For every 1g/L increase in serum albumin the hazard ratio (HR) was 0.91 (95% CI: 0.84, 0.99) (Gariballa et al., 1998a).

Although albumin and pre-albumin are often used in nutritional assessment, the hepatic production of these proteins is down-regulated during periods of acute illness (Gabay and Kushner, 1999); thus, they are often an indicator of illness rather than nutritional status. Other biochemical markers have been used in the evaluation of nutritional assessment, such as serum transferrin, thyroxin binding pre-albumin, retinol binding protein and total lymphocyte count, but they are not specific to nutritional status and/or have poor sensitivity and specificity. Unfortunately, many are affected independently by factors associated with stroke (or any other acute illness), which makes it difficult to assess malnutrition and the response to nutritional interventions (Foley et al., 2012).

Nutrition assessment tools were also used in stroke patients to assess their nutritional status. One study used the "Subjective Global Assessment" tool (Detsky et al., 1987) to identify malnourished patients (16%), who had a poor stroke outcome (as defined by the modified Rankin Scale) and a higher risk of mortality, although the initially significant crude association was no longer statistically significant after adjustment for possible confounders (Davis et al., 2004).

A further development of this tool, the "patient generated subjective global assessment"(Ottery, 2000), was used one year later, in 73 patients admitted to an acute stroke unit (SU) (Martineau et al., 2005). Fourteen (19.2%) patients were identified as being malnourished and, compared to well-nourished patients, they had a significantly longer length of stay (13 vs. 8 days), increased complications (50% vs. 14%), increased frequency of dysphagia (71% vs. 32%) and were more likely to be on modified texture diets (MTD) or enteral feeds (93% vs. 59%). In this study, no association was found between serum albumin level and outcomes or nutritional status.

There appear to be no studies determining the association between risk of malnutrition and outcomes post-stroke. There is one study where patients were screened before entering an intervention trial. Ha et al. examined the effect of individualised nutritional support on weight loss and functional outcomes in stroke patients aged 65 years or older (Ha et al., 2010). However, the assessment of nutritional risk status was carried out using a modified version (by the authors) of a published NST (the "Malnutrition Universal Screening Tool" (Elia et al., 2003)). Furthermore, this original NST was previously validated for other populations, not for stroke (Stratton et al., 2006).

Patients who suffer a stroke can be already malnourished, and a further deterioration of nutritional status after stroke can be explained by several factors.

In a systematic review of 8 studies that examined both swallowing and nutritional status of subjects following a stroke, the odds of being malnourished were increased given the presence of dysphagia (Foley et al., 2009a).

Dysphagia is defined as a difficulty with swallowing, characterised by a reduced coordination of pharyngeal muscles. After stroke, the incidence of dysphagia has been reported to range between 33 to 81% and, if not well managed, dysphagia can lead to aspiration, pneumonia, dehydration, weight loss and malnutrition, among others (Vivanti et al., 2009).

Current guidelines recommend that “people with acute stroke who are unable to take adequate nutrition and fluids orally should receive tube feeding with a nasogastric tube within 24h of admission or be considered for a nasal bridal tube or gastrostomy if they are unable to tolerate a nasogastric tube (…)” (RCP, 2012). As dysphagia improves and the risk of aspiration lessens, MTD can be introduced.

These diets are typically based in distinct consistencies (National Patient Safety Agency Dysphagia Expert Reference Group, 2011), from thin custard consistency to soft and moist foods, which may help to prevent aspiration pneumonia.

However, the nutritional adequacy of MTD has been questioned. Wright and her colleagues found that older people on MTD had a statistically significant lower intake of energy and protein than those consuming a normal hospital diet (Wright et al., 2005). In stroke patients, it was observed that those receiving enteral tube feeding consumed more energy and protein compared with those patients on regular diets or MTD (Foley et al., 2006). Moreover, another study demonstrated that individuals with dysphagia requiring thickened fluids are unlikely to meet any published estimated minimum fluid requirements, unless enteral or parenteral fluids are received (Vivanti et al., 2009).

For those who do not have dysphagia, a wide range of ongoing eating problems and impairments (as a consequence of the stroke) may affect food choices, preparation and consumption. They include upper limb motor/sensory impairment, functionally useless arm, visual/perceptual and communication deficits, lip closure difficulties, chewing difficulties (due to facial weakness), postural instability, etc., which may contribute to the deterioration of nutritional status (Cairella et al., 2004).

At the gastrointestinal (GI) level, ischaemic stroke may disrupt neuronal modulation of oropharyngeal and/or GI motility by interrupting or altering the flow of information from the cortex to the lower regulating centers, which may cause not only the already mentioned dysphagia, but also GI dysmotility and haemorrhage (Schaller et al., 2006). All these factors could also affect nutritional status and stroke recovery. As an example, delayed gastric emptying can cause intolerance to enteral nutrition and compromise the efficacy of drugs administrated by the oral route (Schaller et al., 2006).

The wide range of estimates of malnutrition after stroke might be due to differences in patient characteristics, the definition of malnutrition, as well as the timing and methods of assessment, many of which have not been validated previously (Foley et al., 2009b). To date, no published studies have validated a NST for use specifically in stroke patients (Foley et al., 2012, Cairella et al., 2004, SIGN, 2010).

This justifies the need of finding validated tools for this particular population to identify those patients who are malnourished or at risk of malnutrition and, therefore, more likely to benefit from nutritional interventions.

A small number of studies (Dennis et al., 2006, Gariballa et al., 1998b) tried to evaluate the effect of ONS in acute stroke patients (further information is provided in section 4.6). This nutritional intervention had no significant effect on important outcomes such as death, functional status, LOS and infections, probably because these studies failed to systematically identify patients at risk of malnutrition using a validated method.

As mentioned before, within the non-stroke population, timely nutritional interventions have been shown to result in improved outcomes of nutritionally vulnerable patients (Stratton and Elia, 2007, Kruizenga et al., 2005, Stratton et al., 2003) but there is a lack of good quality evidence in several areas of nutritional support on stroke patients, and the ideal methods and routes of feeding are yet to be determined (Gomes et al., 2014).

1.4 – Obesity and stroke

In 2010, a meta-analysis of prospective studies with 2 million participants, from both Western and Eastern countries analysed the relationship between overweight, obesity, and incidence of ischaemic and haemorrhagic stroke (Strazzullo et al., 2010).

Following a literature search conducted in 3 databases from January 1966 through May 2009, the quality of the studies was evaluated and 25 cohorts were included in this meta-analysis, which had a minimum follow-up period of 4 years and involved participants from 10 countries (from Asia, Europe, United States of America, but not from Africa or Latin America). The quality of the included studies was evaluated by the Downs and Black score system and the authors were satisfied with the fact that all studies had a quality score of at least 15 out of 19. However, the Cochrane Handbook for systematic reviews discourages the use of scales with a scoring system, because calculating a summary score implies the assignment of "weights" to different items in the scale, and it is difficult to justify the weights assigned (Higgins and Altman, 2008) In this systematic review, overall scores are presented for each study, but the detail of the domains missing in each study is not reported.

These authors found that, when compared with the normal weight group (BMI < 25Kg/m^2 for Western populations and BMI < 23Kg/m^2 for Eastern populations), the unadjusted RR for ischaemic stroke was 1.22 (95% CI 1.05-1.41) for overweight and 1.64 (95% CI 1.36-1.99) for obesity. For hemorrhagic stroke, unadjusted RR was 1.01 (95% CI 0.88-1.17) for overweight and 1.24 (95% CI 0.99-1.54) for obesity.

Another set of analyses was conducted, using the RR or HR adjusted for all the confounders included in each study. The number and type of confounders varied between studies, e.g. all of them controlled for the effect of age but not for the effect of oral contraceptives or intake of specific nutrients. This may contribute to the heterogeneity between studies. The significant association between overweight, obesity and risk of ischaemic stroke was maintained, although the strength of the association was attenuated (adjusted RR was 1.18 (95% CI 1.08-1.28) for overweight and 1.50 (95% CI 1.34-1.67) for obesity). The association with hemorrhagic strokes was not statistically significant (adjusted RR was 1.14 (95% CI, 0.96-1.37) for overweight and 1.34 (95% CI, 1.01-1.79) for obesity). When compared with other stroke risk factors, the risk of ischaemic stroke attributed to obesity (OR 1.50, 95% CI

1.34-1.67) is smaller than that posed by diabetes (OR 1.60, 95% CI, 1.29-1.99) or smoking (OR 2.32, 1.91-2.81) or hypertension (OR 2.37, 2.00-2.79) but greater than that associated with heavy alcohol consumption (OR 1.41, 1.09-1.82) (O'Donnell et al., 2010).

Authors also conducted sensitivity analyses and tested these results for evidence of publication bias and heterogeneity (table 1.5) and searched for sources of heterogeneity. None of these factors were identified as significant sources of heterogeneity in the relationship between excess of body weight and ischaemic stroke: gender, age, baseline BMI and blood pressure, year of recruitment or publication and length of follow-up. Geographical origin was not a statistically significant source of heterogeneity (p=0.10) but results suggested that excess of body weight was a better predictor of ischaemic stroke in European and American populations (pooled RR 1.55) than in the Asian individuals (RR 1.08). Moreover, authors used the pooled estimates from random effects models because the tests for heterogeneity were statistically significant in all analyses. These models allow for differences in the treatment effect from study to study and account for unexplained heterogeneity (Riley et al., 2011).

Table 1.5 – Heterogeneity, publication bias and sensitivity analysis, according to groups of total stroke, ischaemic stroke and haemorrhagic stroke (Strazzullo et al., 2010)

	Heterogeneity	**Publication bias**	**Sensitivity analyses**
Overweight vs. normal weight,	Significant ($p<0.001$; $I^2=93\%$)	No conclusive evidence for publication bias	"For both analyses, the stroke risk did not vary substantially with the exclusion of individual studies"
obesity vs. normal weight, and incidence of total stroke	Significant ($p<0.001$; $I^2=91\%$)	Yes (Egger test, p=0.01) but no missing study was identified by the trim-and-fill method	
Overweight vs. normal weight,	Significant ($p<0.001$; $I^2=89\%$)	No (Egger test, p=0.32)	"Sensitivity analysis showed the pooled estimate did not vary substantially with the exclusion of any
obesity vs. normal weight, and incidence of ischaemic	Significant ($p<0.001$;	Yes (Egger test, p=0.002) but no missing study was	

stroke	I^2=88%)	identified by the trim-and-fill method	one study”
Overweight vs. normal weight, **obesity vs. normal weight, and incidence of hemorrhagic stroke**	Significant (p<0.001; I^2=75%) Significant (p<0.001; I^2=75%)	No (Egger test, p=0.18) No (Egger test, p=0.92)	“Sensitivity analysis showed the pooled estimate did not vary substantially with the exclusion of any one study”

Despite the authors recognising the possibility of publication bias, they reinforced the claim in favor of strong educational campaigns focusing on prevention of obesity, due to the statistically significant graded association between excess body weight and incidence of ischaemic stroke (Strazzullo et al., 2010). Two further important limitations of this study were the lack of analysis on the effects of body fat distribution, accounting for the effect of visceral and subcutaneous adiposity and the lack of information in the category of BMI < 25Kg/m^2 (where no distinction was made between normal weight and underweight categories) and the association with risk of stroke.

The relationship between stroke and obesity might be explained by the fact that some modifiable risk factors for stroke are associated with obesity. As mentioned in section 1.1.3, general and abdominal obesity increases the risk of type 2 diabetes, dyslipidemia, hypertension and CHD, which all play an important role in the epidemiology of stroke (Markus et al., 2010). The increased risk of stroke in obesity may also be predicted by the prothrombotic/ proinflammatory state that so often accompanies excessive adipose tissue accumulation (Poirier et al., 2006).

While analysing the effect of obesity on the risk of stroke, some studies find that this was attenuated after adjustment for risk factors such as hypertension, hypercholesterolemia, and glucose intolerance. Nevertheless, Lawlor and her colleagues defend that “as these risk factors are likely to be on the causal pathway between obesity and stroke, the attenuation of effect with their adjustment should not be interpreted as indicating that obesity is not causally related to stroke risk” (Lawlor et al., 2006).

Given this association between obesity and stroke, drawn from observational studies, it would be expected that weight reduction in overweight or obese people should have positive health consequences, lowering the risk of strokes. Thus, a systematic review was conducted to assess the effects of weight reduction for primary prevention (prevention of a first stroke) of stroke in adults with overweight and obesity (Curioni et al., 2009). No trials were found in the literature for inclusion in this review, and therefore, the authors concluded that recommendations for weight reduction in persons with overweight or obesity to prevent a first stroke are still not based on strong scientific evidence. The urgent need for well-designed multi-centre randomised controlled trials assessing this issue was identified.

The current national clinical guidelines for secondary prevention of stroke state that the risk of a recurrent event may vary significantly between individuals according to underlying pathology, comorbidities and lifestyle factors (RCP, 2012).

The same guidelines recommend that patients who are overweight or obese should be advised to lose weight, by receiving advice and support for this purpose (RCP, 2012), although the authors recognise that the evidence in this area of lifestyle measures relates mainly to primary prevention of vascular events.

Furthermore, guidelines of the American Heart Association/American Stroke Association on prevention of stroke in patients with stroke or TIA point out that the complex relationship of obesity and weight to stroke has been studied mostly in relation to primary prevention and no studies have demonstrated that weight reduction reduces risk of stroke recurrence (Furie et al., 2010).

Thus, there is no strong evidence that supports the recommendations for weight loss in overweight and obese individuals who have suffered a stroke.

It is known that there are several nutrients that may potentially influence the risk of stroke (or its risk factors, e.g. hypertension, diabetes, dyslipidemia). Although it was not the purpose of this thesis, the associations (drawn from observational studies) for some key nutrients have been identified:

- Salt

High salt (sodium) intake is associated with an increased risk of stroke (Gardener et al., 2012), possibly because salt has an important role in regulating blood pressure and this is a major stroke risk factor.

- Calcium and vitamin D

Intakes of calcium and vitamin D have been inversely associated with risk of hypertension and risk of stroke (Iso et al., 1999, Wang et al., 2008)

- Fats

Higher intakes of total fat intake and lower levels of PUFAs in erythrocytes have been associated with a higher risk of stroke (Boden-Albala et al., 2009, Park et al., 2009) possibly due to the role that dietary fat has in controlling plasma lipid profile, insulin resistance, glucose intolerance, among others.

- Antioxidants, such as vitamins A, C, E and selenium

Dietary intake of antioxidants has been inversely associated with risk of stroke, possibly due to the role of these nutrients in reducing the reactive oxygen species and reactive nitrogen species, and thus inhibiting the atherosclerotic process (Rautiainen et al., 2012).

The aim of this thesis was to determine the association between nutritional status and outcomes after a stroke. The next three chapters will describe the three studies (of gradually increasing complexity) designed to explore this association, exploring the impact of both malnutrition and obesity.

Chapter 2:

Predictive validity of the Nutrition Screening Tool currently used in Guy’s and St Thomas’ NHS Foundation Trust

2.1 – Introduction

Elderly and stroke patients are particularly susceptible to nutritional depletion, for several reasons. In the elderly population, this might be due to decline in physiological and psychological functions, social determinants, medication, chronic illness or hospitalisation, among others (Brownie, 2006).

As discussed, there are several conditions in stroke patients (in its majority, also elderly), such as perceptual impairment, swallowing disorders or limb weakness, that may reduce the desire and/or the ability to eat (Pennington, 1998). Unless these problems are recognized and managed effectively they can lead to nutritional depletion.

As mentioned before, one way of identifying patients with nutritional problems that might be amenable to nutritional intervention is to use a validated NST.

The differences between nutritional screening (tools) and nutritional assessment (tools) were previously described in chapter 1. This study will only focus on the purpose of screening, since NSTs are advocated as tools that healthcare professionals (who have received training) should be able to use in all health and other care settings including day care, sheltered housing and domiciliary settings (Brotherton et al., 2010). Furthermore, literature presents more studies on the assessment of nutritional status than on the screening of nutritional risk.

The National Institute for Health and Clinical Excellence (NICE) and the British Association for Parenteral and Enteral Nutrition (BAPEN) recommends that all patients should be screened routinely on admission to hospital, at regular intervals throughout their stay and during outpatient and GP appointments (Sizer, 1996, NICE, 2006a). Thus, a NST should be easy to use by health care professionals with little training in nutrition, so all the individuals can be screened, and should be quick to perform, particularly in busy hospital wards. It should also be reliable and valid, since the performance of an instrument is assessed in terms of reliability and validity (Jones, 2006).

Jones describes that “reliability measures the agreement between the results of the tool when administered by different users (inter-rater) or on different occasions (intra-rater). Good agreement when more than one user applies the tool to the same subject, at a similar point in time, implies that use of the tool is not dependent upon the particular user.” The inter-rater reliability has the most relevance for NST, since demonstration of a high inter-rater reliability is enough to consider that the tool is reliable (Jones, 2006).
Validity indicates whether an instrument measures what it purports to do and there are several ways of approaching an assessment of a tool´s validity (Jones, 2006). An important type of validity is the predictive validity or the ability to predict clinical outcomes, with its economic implications (Stratton et al., 2006).

Anthony defends that “a valid screening tool will be appropriate for the targeted population, disorder, diagnosis, or setting and will help demonstrate effectiveness related to positive health outcomes”. On the other hand, using a non validated screening tool may lead to misclassification of patients, which can result in failing to deliver interventions to those who need and/or wasting resources (and possibly cause some harm) on those who do not need (Anthony, 2008).
Thus, a NST should be able to identify patients who are nutritionally at risk, and consequently, more likely to suffer adverse clinical outcomes, in a population with particular characteristics.

The NST currently in use in Guy’s and St Thomas’ NHS Foundation Trust (GSTT NST) (Weekes et al., 2004) was designed based on BAPEN recommendations, which are composed of four questions and two measurements and were proposed by a BAPEN Working Party in 1995 (Lennard-jones et al., 1995). The tool was designed for use within 72 h of admission and weekly throughout a patient’s hospital stay, in order to monitor any changes.

Some types of validity of this tool have previously been assessed in different populations (Weekes and Elia, 2002, Weekes, 2005), as detailed in the “Discussion” section of this chapter, but not the predictive validity for stroke and elderly care patients.

This study was based on a MSc project that was already being carried out in 3 elderly care wards and on the SU of St. Thomas' Hospital (STH).

Details of risk status were obtained from the GSTT NST, during recruitment on the wards by the MSc student, Ms. Aoife Feeney. I was responsible for collecting the follow-up/outcome data (up to one year) on computerised medical records for each recruited patient as well as its statistical analysis.
In particular, I decided which tests would be used depending on the type of variable (e.g. categorical vs. continuous) and on whether data from continuous variables fitted the normal distribution (and, when needed, I log-transformed it), which would determine the use of parametric or non-parametric tests. Initially, I discussed these decisions with both supervisors and one statistician (Mr Peter Milligan) to ensure that I was going in the right direction and making the right interpretation of the results, but all statistical analyses were carried out by the author.
The post-hoc analysis to assess the effect of possible confounders on mortality and LOS was, unfortunately, limited to the baseline data collected by others (Ms Feeney and Ms Prior). This justifies why I have only adjusted the results for the effect of age and gender.

2.2 – Aim and hypothesis

The aim of this study was to assess the predictive validity of the GSTT NST in a group of elderly and stroke patients. This includes the collection of outcomes regarding mortality (primary outcome) and LOS (secondary outcome) during 1 year after recruitment.

The main hypothesis was that the GSTT NST can be used to predict negative outcomes in nutritionally-at-risk stroke and elderly care patients.

In particular, it was hypothesised that there is a significant difference in rates of mortality and LOS (median number of days of all non-elective hospital admissions) between patients in different categories of risk of malnutrition.

2.3 - Methods

2.3.1 – Recruitment, inclusion criteria and ethical considerations

Patients are admitted to the elderly care wards of STH is they are 65 years or older and have age related significant problems such as the geriatric syndromes of falls, incontinence, delirium, dementia or loss of mobility.
During approximately 6 weeks, between the 22nd February and the 15th April 2010, all patients consecutively admitted to the SU and 3 elderly care wards at STH were included in this study. In order to increase the sample size and the power of this study, data previously collected (between the 4th and the 20th of November 2009, on the same wards) by a temporary research dietitian – Ms. Rebecca Prior - were also included in this study.

Ethical approval was obtained from Guy's and St Thomas' NHS Foundation Trust Research Ethics Committee (reference number RJ1 07/0124).
Consent was not required since the study involved undertaking a routine procedure (i.e. nutrition screening) and we were not presenting any patient identifiable data.

All patients consecutively admitted to the wards were included in this study and those who were screened by the nurses were allocated to a nutrition risk category, according to the GSTT NST score:

- low risk (score = 0)
- medium risk (score = 2)
- high risk (equal or greater than 4).

The screening scores and baseline characteristics (e.g. age, gender and pathologies) of patients were collected by Ms. Feeney and Ms. Prior from medical records. Ms. Feeney also assisted in the screening of some patients who were able to stand. She aimed to assess the predictive validity of this NST, considering only 1-month outcomes for those patients she had recruited (n=143). Ms. Prior´s aim was to assess the accuracy and completion rates (by the nurses) of this tool on patients she had recruited (n=65).

The GSTT NST includes questions on recent unintentional weight loss, loss of appetite/decrease in dietary intake, inability to eat for more than 5 days and height and current weight (body mass index) - appendix 2.1. Each question has an associated score. The total score of the sum of the questions is then translated into a level of risk: low or medium or high, as explained above. Patients at high risk should be referred to a dietitian for assessment.

Additionally, if a patient has a BMI < 18.5 Kg/m2 or is on tube feeding or parenteral nutrition or has grade 3-4 pressures sores, he/she should have the same action plan that patients on high risk have, which is the referral to the dietitian, because anyone fulfilling any of these 3 conditions is considered to be at high risk.

This information is collected routinely by nurses for each patient on admission to hospital, including height (that can be measured or recalled) and weight, using *Seca* clinical chair scales or, when not possible, hoist weighing scales available on the ward and calibrated regularly.

When available in the medical notes, the National Institutes of Health Stroke Scale (NIHSS) score for each stroke patient was recorded.

This scale is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. It is valid for predicting lesion size and can serve as an international measure of stroke severity (NIH, 1999-2010). A maximal score of 42 represents the most severe and devastating stroke.

2.3.2 – Follow-up procedure

I conducted the retrospective review of the Trust computerised medical records on the 20th April 2011, to establish each patient's cumulative LOS for all non-elective hospital admissions to STH and mortality (when applicable) at 1 month, 3 months, 6 months and 1 year after admission.

The cumulative LOS is the number resulting from the sum of the days in each non-elective hospital admission, including the initial admission after recruitment, during the follow-up period (up to 1 year), for those patients who survived.

In order to know how the record of deaths is obtained at STH, it was necessary to contact the person responsible for these records. According to the information provided by the Head of Information Analysis at Guy´s and St Thomas´ NHS Foundation Trust (GSTT), he is notified electronically of deaths that occur after discharge, for patients that the Trust has previously treated. A report is run weekly to list deaths of these patients via a NHS number, the "Summary Care Records", using the NHS number of each patient. Thus, collecting mortality data using computerized medical records in this Trust has proven to be a simple and reliable method.

2.3.3 - Statistical analysis

1. Patients were classified into 3 categories of nutritional risk according to GSTT NST score: low, medium and high.
2. The demographic characteristics of patients' in each risk category were compared using the Chi-square test for categorical variables and the one-way analysis of variance (ANOVA) for continuous variables.
3. The Chi-square test was conducted to compare mortality rates between NST risk categories. LOS data were tested for normality using the Kolmogorov-Smirnov test; data that were not normally distributed were log-transformed and tested again for normality. In order to compare LOS (of those patients who survived) between

categories, non parametric tests (e.g. Kruskal-Wallis test) were used for the non-normally distributed data and parametric testes (e.g. ANOVA) were used on data that fitted the normal distribution.

4. A post-hoc analysis to assess the effect of possible confounders (e.g. age and sex) on mortality and LOS (ranked or log-transformed) included a binary logistic regression and univariate analysis of variance.

5. The data were also analysed by combining the 3 GSTT nutrition risk categories into 2 categories (low and medium vs. high; low vs. medium and high).

Data were analysed using SPSS software version 19.0 for Windows (Chicago**,** Illinois**,** USA). Any differences were considered statistically significant when $p < 0.05$.

2.4 – Results

From a total of 208 patients admitted to the wards, 65 were recruited in November 2009 and 143 were recruited in March and April 2010. From the total of 208 patients included in this study, only 182 (87.5%) had the GSTT applied on admission. Reasons for not screening may include the patient being discharge before screening and severity of illness, i.e., when the patient was not supposed to receive any active treatment due to entry on the Liverpool Care Pathway.

Differences between patients who had and had not the GSTT NST applied on admission are shown in table 2.1. There were no statistically significant differences regarding gender and age between the groups (*p=0.140* and *p=0.265*, respectively), which suggests that the sample used to assess the predictive validity of the NST did not present a selection bias, in relation to these characteristics.

Table 2.1 – Characteristics of patients who were and were not screened for the risk of malnutrition

Patients screened vs. not screened	n (%)	Age [a] Mean, in years (SD)	Minimum – Maximum (years)	Sex [b] Female, n (%)	Male, n (%)
Patients screened	182 (87.5%)	75.4 (16.6)	25 – 106	98 (54%)	84 (46%)
Patients not screened	26 (12.5%)	79.1 (16.2)	31 – 96	18 (69%)	8 (31%)
Total	208 (100%)	75.8 (16.6)	25 – 106	116 (56%)	92 (44%)

[a] - ANOVA, *p=0.265*

[b] - Chi-square test, *p=0.140*

Table 2.2 shows the categorisation of patients in each nutritional risk category, and their characteristics with regards to age, gender and BMI. The mean age was 75 years, in a group that included patients from 25 to 106 years, with 54% being women.

Table 2.2 – Patient characteristics according to malnutrition risk

GSTT NST risk categories	n (%)	Age [a]		Sex [b]		Body mass index	
		Mean, years (SD)	Minimum – maximum (years)	Female, n (%)	Male, n (%)	Mean, Kg/m^2 (SD)	Minimum – maximum (Kg/m^2)
Low risk	91 (50%)	72.9 (17.6)	27 – 98	50 (55%)	41 (44.6%)	25.9 (4.7)	18.6 – 41.9
Medium risk	33 (18%)	73.1 (18.2)	25 – 98	18 (55%)	15 (45%)	25.2 (3.8)	19.0 – 34.9
High risk	58 (32%)	80.2 (12.9)	39 – 106	30 (52%)	28 (48%)	20.8 (4.9)	13.0 – 40.8
Total	182 (100%)	75.3 (16.6)	25 – 106	98 (54%)	84 (46%)	24.2 (16.6)	13.0 – 41.9

[a] - ANOVA, *p=0.024*

[b] - Chi-square test, *p=0.925*

Fifty eight (32%) patients were categorised as being at high risk of malnutrition, and this was the group that presented the highest mean age and the lowest mean BMI. The greater the NST risk, the higher was the mean age, with a statistically significant difference between the mean age of each group ($p=0.024$).

The distribution of patients according to gender in each NST risk category was similar ($p=0.925$).

With regards to the diagnoses of the individuals, there was a wide range of pathologies, with many patients presenting multiple diseases, which prevented the analysis of diseases prevalence. Some examples of the pathologies mentioned in the medical records included vitamin B12 deficiency, constipation, hypertension, type 2 diabetes mellitus, shortness of breath due to stage 4 metastatic lung cancer, exacerbation of chronic obstructive pulmonary disease, renal failure, unexplained falls, anaemia, acute confusional state secondary to urinary tract infection, community acquired pneumonia, viral illness, etc.

Some of the individuals in this study were recruited from the SU but not all of those admitted at the SU received a diagnosis of stroke.

The number of patients who were diagnosed as having a stroke in this admission was too small (n=25, 14%) for a valid statistical analysis of the predictive validity of the GSTT in stroke alone. However, the baseline characteristics of this group of patients, according to malnutrition risk, are presented below.

Table 2.3 – Baseline characteristics of patients who had a stroke in this admission, according to malnutrition risk

GSTT NST risk categories	n (%)	Age [a]		Sex [b]		BMI	
		Mean, years (SD)	Minimum – maximum (years)	Female, n (%)	Male, n (%)	Mean, Kg/m^2 (SD)	Minimum – maximum (Kg/m^2)
Low risk	16 (64%)	69.3 (14.5)	46 – 90	7 (44%)	9 (56%)	26.4 (4.8)	19.7 – 34.6
Medium risk	5 (20%)	64.6 (19.5)	42 – 90	3 (60%)	2 (40%)	23.1 (3.0)	19.0 – 27.5
High risk	4 (16%)	78.8 (10.4)	63 – 85	1 (25%)	3 (75%)	23.6 (4.01)	17.7 – 27.1
Total	25 (100%)	69.8 (15.1)	42 – 90	11 (44%)	14 (56%)	24.2 (16.6)	17.7 – 34.6

[a] - ANOVA, *p=0.394*

[b] - Chi-square test, *p=0.575*

The distribution of patients according to age and gender in each NST risk category was not significantly different (*p=0.394 and p=0.575*, respectively), although those classified at high risk of malnutrition tended to be older.

The proportion of patients at high risk of malnutrition was lower in comparison with the entire group of 182 individuals. This may be due to the different characteristics of the population (stroke vs. mainly elderly) but these results should be interpreted with caution, due to the small sample size of the group of patients who had a stroke.

Predictive validity of the GSTT NST

1. Mortality

When the analyses for the first outcome measure were performed, there was a significant difference in mortality rates between patients in the three malnutrition risk categories at all time points (*p=0.011* at 1 month, *p=0.002* at 3 months, *p=0.001* at 6 months and *p<0.001* at 1 year) - table 2.4 and fig 2.1.

Mortality rates increased progressively with malnutrition risk category (fig. 2.1). One month after admission, those identified as at high risk of malnutrition had, at least, a four-fold increased rate of mortality compared with those at low and medium risk. At 3 months, 6 months and 1 year, rates of mortality of patients at high risk of malnutrition were, at least, 2 times higher than the rates of mortality of patients at low and medium risk.

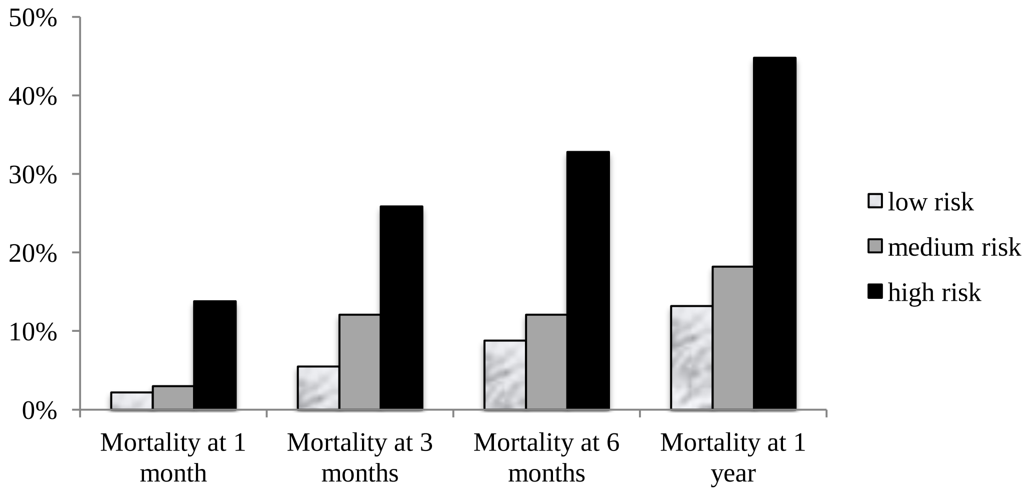


Fig. 2.1 – Rates of mortality in each GSTT NST risk category, at all periods of follow-up (data extracted from table 2.4).

Table 2.4 - Mortality data for each GSTT NST risk category at 1month, 3 months, 6 months and 1 year after admission.

Risk of malnutrition		Mortality at 1 month [a]		Total	Mortality at 3 months [b]		Total	Mortality at 6 months [c]		Total	Mortality at 1 year [d]		Total
		Alive	**Dead**		**Alive**	**Dead**		**Alive**	**Dead**		**Alive**	**Dead**	
low risk	**n**	89	2	91	86	5	91	83	8	91	79	12	91
	(%)	97.8%	2.2%	100%	94.5%	5.5%	100%	91.2%	8.8%	100%	86.8%	13.2%	100%
medium risk	**n**	32	1	33	29	4	33	29	4	33	27	6	33
	(%)	97.0%	3.0%	100%	87.9%	12.1%	100%	87.9%	12.1%	100%	81.8%	18.2%	100%
high risk	**n**	50	8	58	43	15	58	39	19	58	32	26	58
	(%)	86.2%	13.8%	100%	74.1%	25.9%	100%	67.2%	32.8%	100%	55.2%	44.8%	100%
Total	**n**	171	11	182	158	24	182	151	31	182	138	44	182
	(%)	94.0%	6.0%	100%	86.8%	13.2%	100%	83.0%	17.0%	100%	75.8%	24.2%	100%

[a] - Chi-square test, $p=0.011$
[b] - Chi-square test, $p=0.002$
[c] - Chi-square test, $p=0.001$
[d] - Chi-square test, $p<0.001$

Binary logistic regression was used to determine the risk of mortality for each GSTT NST risk category (using low risk as the reference group) in the unadjusted models, and to investigate the effects of age and gender in the association between these 2 variables in the adjusted models, at each time point - table 2.5. In the adjusted model, the low risk of malnutrition is the reference group, men are compared with women (reference group) and age is treated as a continuous variable.

In the adjusted models, at 1 and 3 months, neither of these possible confounders was found to be significant in the final model, i.e., the variables age and sex were not significant predictors of mortality. At 6 months and 1 year, age had a significant effect on mortality ($p=0.018$ and $p<0.001$) but it did not affect the significant association between risk of malnutrition and mortality. At 3 months, 6 months and 1 year, this association between nutrition risk status and mortality remained significant (and was nearly significant at 1 month) after taking into consideration the effect of age and gender ($p=0.057$ at 1 month, $p=0.013$ at 3 months, $p=0.006$ at 6 moths and $p=0.001$ at 1 year) (see table 2.5). At 1 month, the trend for a statistically significant association between risk of malnutrition and mortality (and the wide confidence intervals observed in each group) may be explained by the relatively low number of deaths (6% at 1 month vs. 13.2% at 3 months, 17% at 6 months and 24.2% at 1 year).

Table 2.5 – Logistic regression of the association between risk of malnutrition and mortality, unadjusted and adjusted for the effect of age and gender, in different periods of time

Outcome	**Predictor variable**	**Unadjusted model (OR, 95% CI)**	**p value**	**Adjusted model (OR, 95% CI)**	**p value**
Mortality at 1 month	**Risk of malnutrition**		0.028		0.057
	Low	Reference group		Reference group	
	Medium	1.39 (0.12-15.86)	0.791	1.39 (0.12-15.94)	
	High	7.12 (1.46-34.84)	0.015	5.98 (1.21-29.70)	
	Gender (male)	_	_	1.16 (0.31-4.35)	0.827
	Age (per 1-year increase)	_	_	1.04 (0.98-1.10)	0.204
Mortality at 3 months	**Risk of malnutrition**		0.004		0.013
	Low	Reference group		Reference group	
	Medium	2.37 (0.60-9.44)	0.220	2.43 (0.60-9.80)	
	High	6.00 (2.05-17.60)	0.001	5.14 (1.72-15.36)	
	Gender (male)	_	_	0.72 (0.28-1.84)	0.488
	Age (per 1-year increase)	_	_	1.04 (0.99-1.08)	0.074
Mortality at 6 months	**Risk of malnutrition**		0.001		0.006
	Low	Reference group		Reference group	
	Medium	1.43 (0.40-5.11)	0.581	1.46 (0.40-5.31)	
	High	5.05 (2.04-12.55)	<0.001	4.27 (1.68-10.86)	
	Gender (male)	_	_	0.77 (0.33-1.81)	0.547
	Age (per 1-year increase)	_	_	1.05 (1.01-1.09)	0.018
Mortality at 1 year	**Risk of malnutrition**		<0.001		0.001
	Low	Reference group		Reference group	
	Medium	1.46 (0.50-4.28)	0.487	1.52 (0.49-4.67)	
	High	5.35 (2.41-11.88)	<0.001	4.62 (1.99-10.73)	
	Gender (male)	_	_	1.04 (0.48-2.26)	0.926
	Age (per 1-year increase)	_	_	1.08 (1.03-1.12)	<0.001

OR = Odds ratio

2. Length of hospital stay

Distribution of LOS (secondary outcome) at 1 month, 3 months, 6 months and 1 year were analysed with histograms and Q-Q plots. Data were tested for normality and, as anticipated from the literature, they were not normally distributed (Kolmogorov-Smirnov test, $p<0.001$, at all time points).

LOS data at 4 time points were log-transformed (which could help mitigate the skewness) and tests for normality were repeated. This revealed that the log-transformed LOS at 1 month continued to be not normally distributed (Kolmogorov-Smirnov test, $p=0.001$) but the log-transformed LOS at 3 months, 6 months and 1 year follows a normal distribution (Kolmogorov-Smirnov test, $p=0.200$).

Non-parametric tests were used therefore, to explore differences on LOS at 1M between categories and parametric tests were used for the other follow-up periods.

As ANOVA assumes that the data come from populations that have equal variances, the assumption for equal variances was tested using the Levene's test ($p > 0.05$ in all time points).

As shown in table 2.6, the distribution of LOS at 1 month was significantly different across categories of risk of malnutrition (Kruskal-Wallis test, $p=0.034$). LOS (of patients who did not die within the first month) increased progressively with malnutrition risk category, from a median of 12 to 16 days.

At 3 months, 6 months and 1 year, there were no statistically significant differences in the LOS between the risk categories (ANOVA, $p=0.062$, $p=0.057$ and $p=0.270$, respectively). However, the trend for a longer LOS in the high risk group was maintained at all follow-up periods (and the differences at 3 and 6 months approached significance).

Table 2.6 – Length of hospital stay in each GSTT NST risk category, for those patients who survived at 1 month, 3 months, 6 months and 1 year

Length of hospital stay (LOS)		**LOS at 1 month [a] n=171**	**LOS at 3 months [b] n=158**	**LOS at 6 months [c] n=151**	**LOS at 1 year [d] n=138**
		Median (range)	Mean (SD) (range)	Mean (SD) (range)	Mean (SD) (range)
Risk of malnutrition	**low risk**	12 (1-30)	12.9 (2.7) (1-90)	14.7 (2.8) (1-132)	17.1 (3.1) (1-196)
	medium risk	13.5 (2-30)	15.2 (2.6) (2-90)	17.4 (2.8) (2-132)	21.3 (2.7) (2-132)
	high risk	16 (3-30)	19.5 (2.2) (4-66)	23.3 (2.3) (5-80)	23.7 (2.2) (5-73)

Mean (SD) values are presented as the anti-logged mean (SD) of the log-transformed data

[a] - *Kruskal-Wallis test, p=0.033*

[b] - *ANOVA, p=0.062*

[c] - *ANOVA, p=0.057*

[d] - *ANOVA, p=0.270*

The visual representation of the LOS data distribution can be found in the following box plots (fig. 2.2, 2.3, 2.4 and 2.5).

In each figure, the bottom and top of the box are the 25th and 75th percentile (the lower and upper quartiles, respectively), and the band near the middle of the box is the 50th percentile (the median). The ends of the vertical lines or "whiskers" indicate the minimum and maximum data values, excluding outliers. The circles and asterisks above the upper “whisker” represent the outliers, which can be defined as any data point more than 1.5 times the interquartile range beyond the relevant quartile.

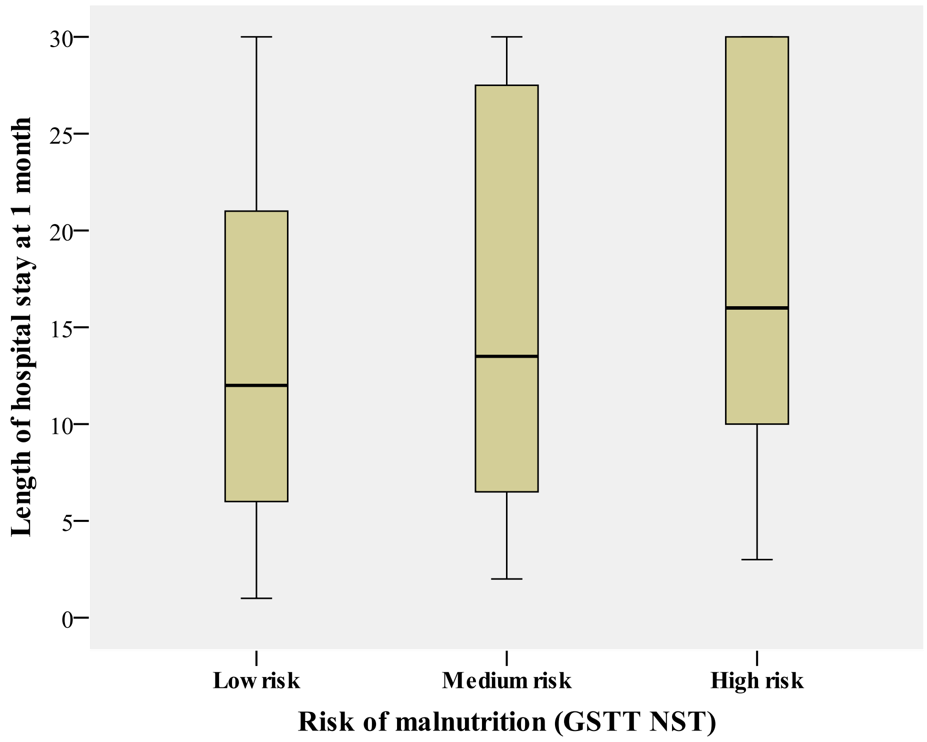


Fig. 2.2 - Distribution of data regarding the LOS in each GSTT NST risk category, at 1 month

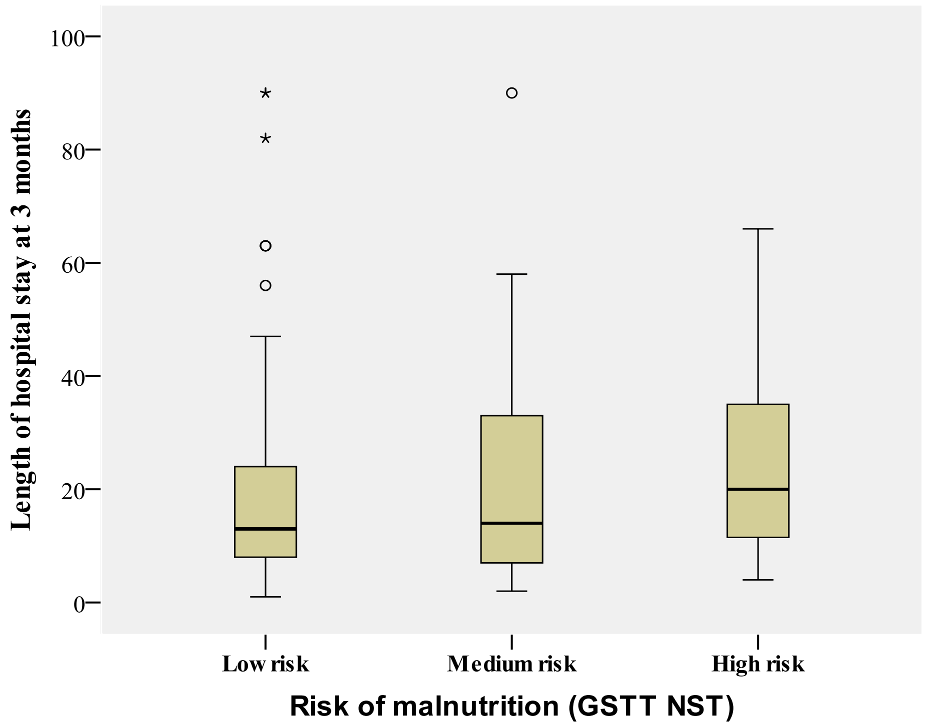


Fig. 2.3 - Distribution of data regarding the LOS in each GSTT NST risk category, at 3 months

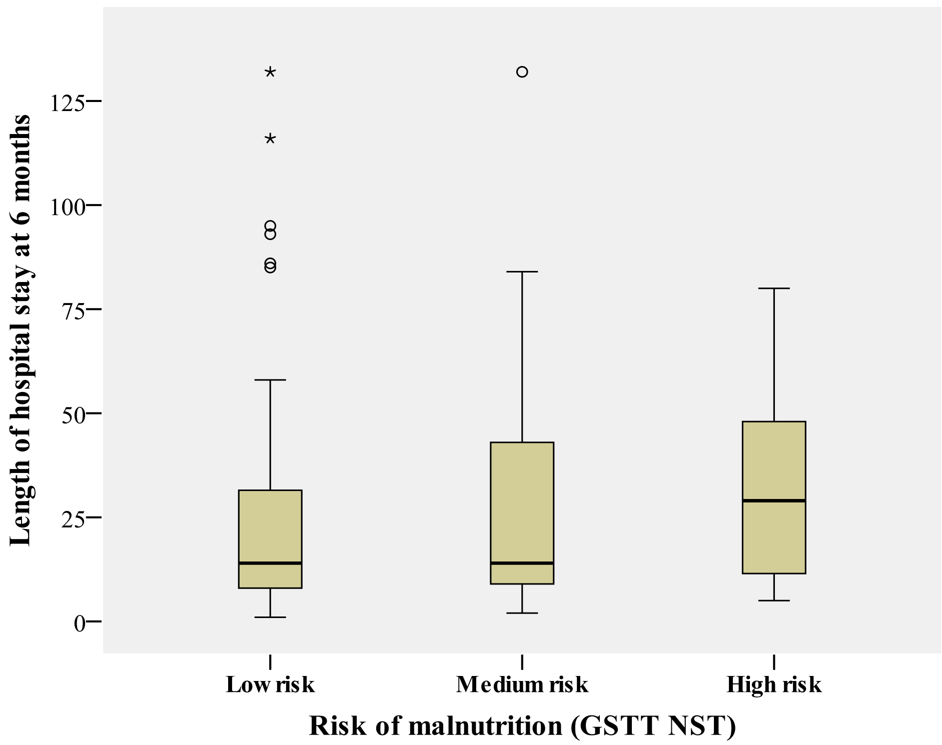


Fig. 2.4 - Distribution of data regarding the LOS in each GSTT NST risk category, at 6 months

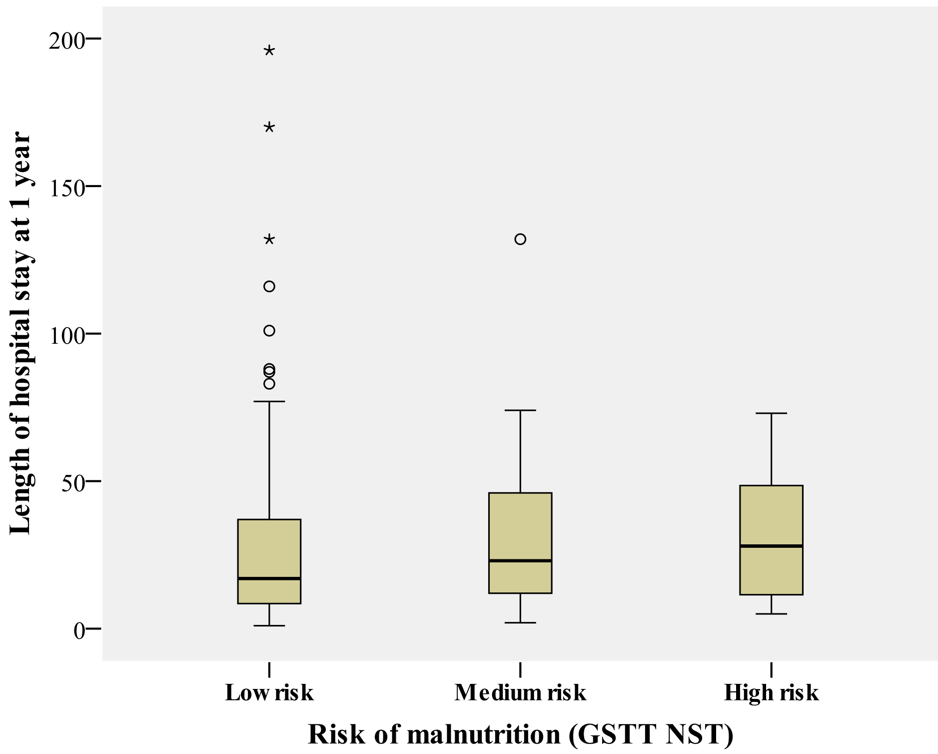


Fig. 2.5 - Distribution of data regarding the LOS in each GSTT NST risk category, at 1 year

The effects of age and gender on the relationship between the GSTT NST risk categories and the ranked LOS at 1 month or the log-transformed LOS at 3 months, 6 months and 1 year, were investigated using univariate analysis of variance (table 2.7).

The initial significant association between the GSTT NST risk categories and LOS at 1 month was attenuated (*p=0.156*) after taking into consideration the effects of age and gender, where age was a significant predictor of LOS (*p<0.001)*.

The association between risk categories and the log-transformed LOS at 3, 6 and 12 months remained non-significant (*p=0.246*, *p=0.259* and *p=0.405*, respectively), but age was shown to have a significant effect on this outcome (*p<0.001*, at all time periods).

Table 2.7 – Association between risk of malnutrition and ranked or log-transformed LOS, adjusted for the effect of age and gender (univariate analysis of variance), at different periods of time

Outcome	**Predictor variable**	**F**	***p* value**
Ranked LOS at 1 month	Risk of malnutrition	1.88	0.156
	Gender	0.86	0.356
	Age	25.89	<0.001
Log-transformed LOS at 3 months	Risk of malnutrition	1.42	0.246
	Gender	0.53	0.467
	Age	26.87	<0.001
Log-transformed at 6 months	Risk of malnutrition	1.36	0.259
	Gender	0.83	0.365
	Age	28.06	<0.001
Log-transformed at 1 year	Risk of malnutrition	0.91	0.405
	Gender	0.21	0.652
	Age	32.45	<0.001

The data were also analysed by combining the 3 GSTT NST nutrition risk categories into 2 categories (low and medium vs. high; low vs. medium and high). The results were similar to the findings described so far, i.e., there was a statistically significant difference in rates of mortality at all time points between the risk categories (table 2.8), even after the adjustment for the effect of age and gender ($p<0.05$ in all periods of time, using logistic regression – data not shown).

Differences in LOS (median or mean number of days) were significant at 1, 3 and 6 months between malnutrition risk categories (table 2.9), but were no longer significant after the adjustment for the effect of age and gender ($p>0.05$ in all periods of time, using univariate analysis of variance – data not shown).

Table 2.8 – Mortality rates for each GSTT NST risk category (divided in 2 groups) at 1month, 3 months, 6 months and 1 year after admission.

Risk of malnutrition		**% of deaths at 1 month**	**Chi-square test (p value)**	**% of deaths at 3 months**	**Chi-square test (p value)**	**% of deaths at 6 months**	**Chi-square test (p value)**	**% of deaths at 1 year**	**Chi-square test (p value)**
Low/medium	**n**	3	0.003	9	0.001	12	<0.001	18	<0.001
risk (n=124)	**(%)**	2.4%		7.3%		9.7%		14.5%	
High risk	**n**	8		15		19		26	
(n=58)	**(%)**	13.8%		25.9%		32.8%		44.8%	
Low risk	**n**	2	0.000	5	0.002	8	0.003	12	0.001
(n=91)	**(%)**	2.2%		5.5%		8.8%		13.2%	
Medium/high	**n**	9		19		23		32	
risk (n=91)	**(%)**	9.9%		20.9%		25.3%		35.2%	

Table 2.9 – Length of hospital stay in each GSTT NST risk category (divided in 2 groups), for those patients who survived at 1 month, 3 months, 6 months and 1 year.

Risk of malnutrition	**LOS at 1 month n=171**		**LOS at 3 months n=158**		**LOS at 6 months n=151**		**LOS at 1 year n=138**	
	Median (range)	Mann-Whitney test (p value)	Mean (SD) (range)	t-test (p value)	Mean (SD) (range)	t-test (p value)	Mean (SD) (range)	t-test (p value)
Low/medium	12 (1-30)	0.014	13.5 (2.6) (1-90)	0.027	15.4 (2.8) (1-132)	0.013	18.1 (3.0) (1-196)	0.128
High	16 (3-30)		19.5 (2.2) (4-66)		23.3 (2.3) (5-80)		23.7 (2.2) (5-73)	
Low	12 (1-30)	0.021	12.9 (2.7) (1-90)	0.037	14.7 (2.8) (1-132)	0.039	17.1 (3.1) (1-196)	0.191
Medium/high	15.5 (2-30)		17.6 (2.3) (2-90)		20.6 (2.5) (2-132)		22.5 (2.4) (2-132)	

Mean (SD) values are presented as the anti-logged mean (SD) of the log-transformed data

2.5 – Discussion

This is the first study to evaluate the predictive validity of the GSTT NST in a group of hospitalised elderly and stroke patients, over a period of up to 1 year.

Independently of the method chosen to group risks of malnutrition, i.e., 3 categories or 2 categories (low and medium vs. high; low vs. medium and high), the results take the same direction: patients in the medium and high risk categories had more negative clinical outcomes, i.e. a significantly higher rate of mortality and a trend for an increased LOS.

As discussed in chapter 1, the literature shows that malnourished patients have increased LOS and increased mortality when compared with well-nourished patients.

These parameters may, therefore, be used to test the predictive validity of a NST, and they are frequently used in studies with this purpose (Jones, 2002, Stratton et al., 2006). The ability to predict mortality and a longer LOS would suggest that a nutrition score has real prognostic value and is correctly identifying those patients who are more likely to suffer adverse outcomes.

Mortality and LOS are important factors, not only for the patient but also for the NHS, since mortality and a longer LOS poses a great economic burden on the NHS. Furthermore, these variables were also chosen as relevant outcomes to study the predictive validity of this tool because they are easily and reliably collected by the computerised medical records, for all patients.

In this study, the proportion of patients categorised as being at high risk of malnutrition was 32%, which is similar to the 35% found in older hospitalised patients using the MUST (Henderson et al., 2008). In hospitalised stroke patients, a similar prevalence of malnutrition was found - 32% (Westergren et al., 2001b) and 26.3% (Crary et al., 2006), although the authors used nutrition assessment rather than NSTs.

It should be noted that the medium and high risk categories included patients who had a normal weight and also those who were overweight and obese, as the maximum BMI values in these groups were 34.9 Kg/m^2 and 40.8 Kg/m^2, respectively. This contradicts the idea that only underweight individuals are malnourished or at high risk of malnutrition and, consequently, it does not support the use of a subjective evaluation of patients' nutritional status (based purely on simple observation), which has been reported in previous studies (Dennis et al., 2006).

No statistically significant difference in LOS was found between the risk categories at 3 months, 6 months and 1 year, and the statistically significant difference on LOS at 1 month initially observed disappeared after the adjustment for the effect of age. There are several reasons that can explain these results.

First, it is possible that LOS might be influenced by different circumstances unrelated to nutritional status, such as, the waiting time for transfer to a rehabilitation facility or a nursing home. This may be the case of, for example, the individuals who stayed in the hospital for a very long continuous period of time, i.e. more than 4 months (132 days) within only one admission, when the censoring point was 6 months.

Second, age might be a more important factor than NST risk category to predict LOS, although it can be argued that these factors are interlinked. There are several physiological functions that tend to decline with age and can have a negative impact on nutritional status. This includes a reduction of lean body mass and metabolic rate, decreased gastrointestinal motility and secretion of digestive juices, changes in the oral cavity (such as loss of teeth and reduced salivary secretion), sensory function deficits (e.g. diminished sense of taste), changes in fluid and electrolyte regulation (e.g. reduced glomerular filtration rate), multiple chronic diseases and polypharmacy (Brownie, 2006). Consequently, a poor nutritional status may delay the recovery during hospitalisation and favor the occurrence of new infectious diseases (since the immune system is compromised by inadequate nutrition), which increases even more the LOS.

Third, it is also possible that there is no causal relationship between nutritional status and LOS, since LOS may be predominantly a reflection of the severity of the underlying disease, instead.

It should be noted that LOS was measured only in people who escaped from the first and worse outcome, i.e., death. Those who survived and were at medium and high risk of malnutrition still presented a trend for a longer LOS than those who were classified as being at low risk of malnutrition.

Additionally, this study had a relatively small sample size and a heterogeneous population.

Several aspects of validity and reliability of this NST were already studied, as summarized in the next table.

Table 2.8 – Type of assessments previously conducted on the GSTT

Type of assessments	Population	References
inter-rater reliability	- general medical inpatients - respiratory outpatients	(Weekes, 2005)
concurrent validity	- general medical and elderly inpatients	(Weekes and Elia, 2002)
predictive validity	- respiratory outpatients - medical inpatients	(Weekes, 2005)

The inter-rater reliability was studied in general medical inpatients and respiratory outpatients to see whether different examiners (nurse vs. nurse and nurse vs. doctor) reliably identify the same nutritionally at risk patients, using this tool. A good inter-rater reliability ($\kappa = 0.67$) was observed between pairs of nurses on general medical inpatients and a very good inter-rater reliability ($\kappa = 0.94$) between the nurse and doctor´s assessment on respiratory outpatients (Weekes, 2005).

The concurrent validity, which is one way of establishing validity by comparing different methods of screening, was assessed in general medical and elderly inpatients. The results suggested good/very good concurrent validity between this tool and the Malnutrition Advisory Group Tool (Elia, 2000) and very good concurrent validity between each of these and the assessment made by the dietitian (Weekes and Elia, 2002).

The predictive validity of this tool was tested in general medical inpatients and respiratory outpatients, using mortality and LOS as relevant negative outcomes and a follow-up period of twelve months (Weekes, 2005).
On medical inpatients, a higher proportion of patients died within one year in the higher risk categories, similar to the findings observed in the current study, for the elderly and stroke patients. However, the present study showed a graded association between risk of malnutrition and mortality, while the mortality of medical inpatients was surprisingly higher on the medium risk group (32% of deaths at 1 year on the medium risk groups vs. 17% on the high risk group).
Weekes found statistically significant differences in the mean LOS between the risk categories, even after controlling for the effect of age. The current study found the same tendency (but not a significant difference) for a longer LOS in higher risk categories of malnutrition. The potential reasons for the lack of statistical significance have already been discussed.

In respiratory outpatients, the findings of Weekes 2005 are similar to those described for the medical inpatients. The differences for both outcomes were statistically significant between the risk categories and, for both patient groups, LOS was at least two-fold higher in medium or high risk patients compared with low risk patients.
Mortality rates in respiratory outpatients also presented a graded increase in nutrition risk categories, where those identified as being at high risk had at least a three-fold increase in mortality compared with those at low risk (Weekes, 2005), similar to what happened in the elderly and stroke population (at all time points).

Therefore, this NST seems to have a similar performance to predict mortality in different populations (respiratory outpatients, medical inpatients and elderly and stroke inpatients).

Nonetheless, validity is a continuous process and the predictive validity of this NST needs to be established in other patient groups and healthcare settings.

This study had several limitations, which are as follows:

- data collection procedures were not standardised and, therefore, the level of detail and possibly the quality of the data were not the same between the 2 investigators (Ms. Feeney and Ms. Prior)
- the nutritional interventions that patients received while in hospital were not taken into consideration. These interventions, if appropriate, could have the potential to modify the outcomes. However, this would be difficult to measure and it has not been taken into consideration in previous studies on the association between nutritional status or risk and outcomes
- the study did not capture (LOS of) admissions that may have occurred in other hospitals
- only 183 patients (88%) were screened on admission, and there is no information available regarding the reason why 12% of the recruited patients were not screened. This study was conducted on elderly care and stroke wards, which manage severely frail, disabled individuals who are bed-bound. It is possible that the non-screened patients had these characteristics and this study was lacking the associated clinical outcome of this potentially vulnerable patient group. However, both groups presented a similar mean age and proportion of genders, suggesting that they had similar characteristics.
- this was a pilot-study and may, therefore, have been underpowered. The number of stroke patients was too small to allow for a separate analysis of the GSTT NST predictive validity in this particular population and results were not adjusted for an important possible confounder, i.e., the severity of stroke (as this information was obtained for only 5 out of 25 patients who had a stroke)

Contributions and lessons learnt from this study

Despite its limitations, this study was very useful to obtain information about the practicalities of data collection, to refine the techniques and to inform the design of future studies. It also had the advantages of showing the evolution of the outcomes at several time-points, from one month up to one year, and it captured mortality and LOS (of other admissions) that may have occurred after discharge, while previous studies contained information on outcomes concerning only the first hospitalisation (from screening to discharge or death (Raslan et al., 2010, Raslan et al., 2011)).

In particular, this study enabled me to:

- have the first contact with the UK research fieldwork (e.g. become familiar with abbreviations used in medical notes and tools available for data collection), on busy wards that care for frail and severely ill patients. This was also the first time I was exposed to a new national health service and its nutrition screening practices
- realise that NST are widely used and advocated as fundamental tools that should be applied to all patients on admission to hospital, but not all patients actually have the NST applied by the nursing staff, and when it is applied, it is usually incomplete (e.g. weight on admission may be recorded but patient's usual weight is not)
- understand how outcome data can be accurately and systematically collected. With respect to mortality, I realised that the computerised medical records at GSTT are a simple and reliable method to obtain mortality data (after consulting the Head of Information Analysis of this Trust). With regard to cumulative LOS, I realised that collecting information on every admission to GSTT that 182 patients had over several time periods (1 month, 3 months, 6 months and 1 year) is a very time consuming task and susceptible to human error, especially when this is done manually, not through an automated process.
- realise that computerised medical records provide mortality information held nationally but hospital (re)admissions data is only related to admissions that occurred at GSTT. Thus, if a patient is readmitted to another hospital in England while on holiday or if the patient is transferred to another hospital post-discharge from GSTT, I am not able to capture that information
- recognise that the quantity and quality of potential confounders collected in this study is not enough. For example, ethnicity and smoking data could have been collected, and not all stroke patients had the NIHSS applied. This is a limitation of working with (baseline) data collected by someone else.
- become familiar with statistical analyses, data handling and transformation (e.g. choose adequate tests for normally and not normally distributed data), which will be later used in chapter 4
- become aware of the time required to recruit stroke patients from the Stroke Unit of St. Thomas´s Hospital (and the number that I can potentially achieve within my PhD)

- although many other studies that have assessed the predictive validity of NST or nutrition assessment tools are usually conducted in heterogeneous populations (e.g. patients recruited from multiple medical specialities (Raslan et al., 2010, Correia and Waitzberg, 2003) or elderly care wards (Stratton et al., 2006, Henderson et al., 2008)), this study enabled me to understand that it becomes difficult to take into account the effect of the disease on outcomes in a sample that includes individuals with very different type and severity of diseases.

Thus, I learnt that in a future, prospectively designed, study (chapter 4), I will need to:
- apply the NST myself to all patients on ward (this may include weigh the patient myself and collect information from multiple sources)
- increase the sample size of stroke patients and do a power calculation to determine the size of the sample needed
- allow for enough time to recruit a large sample size of patients with a diagnosed acute stroke and consider expanding my research sites to achieve that target
- find a way of capturing data regarding hospital admissions that occur nationally and, ideally, in an automated process (such as the Hospital Episode Statistics)
- have a thorough selection of potential confounders and make an effort to collect information regarding each confounder for every patient

2.6 – Conclusion

In studies that explore the association between (risk of) malnutrition and outcomes in heterogeneous populations (e.g. those that include a comprehensive range of several medical specialties (Middleton et al., 2001, Correia and Waitzberg, 2003, Raslan et al., 2010)), it is difficult to distinguish the effect of disease from the effect of malnutrition on outcomes. In fact, malnutrition and disease are interrelated and both may contribute to worse clinical outcomes.

Although the present findings suggest that the GSTT NST can be used to predict negative outcomes in the elderly and stroke hospitalised population, more research is needed to make definitive conclusions. Therefore, an adequately powered study was designed to investigate the predictive validity of NSTs in patients who have had a stroke (chapter 4).

Chapter 3:

The association between BMI and mortality after a first-ever stroke: a cohort study within the South London Stroke Register

3.1 - Introduction

As mentioned in chapter 1, obesity has been established as a stroke risk factor (Strazzullo et al., 2010, Wang et al., 2013) and the current guidelines for secondary prevention of stroke recommend patients who are overweight or obese should be advised to lose weight (RCP, 2012, AHA, 2009). Recent studies however, suggest a protective effect of a high BMI in terms of mortality in particular populations, including the stroke population - a phenomenon that has been called “the obesity paradox”.

Landi et al studied the effect of age on the relationship between BMI and mortality in a large cohort of hospitalized patients with a wide range of diseases (Landi et al., 2000). The authors found that the graphed relationship between BMI and mortality in younger patients (aged under 65 years) was typically hyperbolic (U-shaped), with increased risk of mortality at the lowest and highest BMIs. However, the older patients (aged 65 years and over) showed an increased risk of mortality at the lowest BMIs with only a slight elevation for the heaviest group (BMI > 35 kg/m^2), supporting the hypothesis that the optimal weight for longevity may be higher in older patients.
Nevertheless, this relationship between BMI and mortality seems to be, not only age-dependent, but also ethnicity-dependent.
A large pooled analysis with more than 1 million Asians (likely to include healthy and diseased individuals) (Zheng et al., 2011) revealed a U-shaped association between BMI and mortality in East Asians (including Chinese, Japanese and Koreans), similarly to the pattern observed in white adults (Berrington de Gonzalez et al., 2010). On the other side, in the cohorts of Indians and Bangladeshis there was no excess risk of mortality associated with a high BMI, suggesting a J-shaped curve (Zheng et al., 2011).

Furthermore, this “reverse epidemiology” of the association between BMI and mortality (where obesity may, counterintuitively, be protective) has also been described in several diseases, such as rheumatoid arthritis (Kremers et al., 2004), chronic obstructive pulmonary disease (Landbo et al., 1999), chronic kidney disease (stages 3 and 4 (Kovesdy et al., 2007)), hypertension and coronary artery disease (Uretsky et al., 2007) and, more recently, diabetes (Carnethon et al., 2012).

According to Kalantar-Zadeh and his colleagues, these paradoxical associations between better survival in more obese persons have been observed in chronic disease states and advanced age, which are populations with a shorter life expectancy than the general population and with greater likelihood of wasting and cachexia (Kalantar-Zadeh et al., 2007).

The stroke population does not seem to be an exception. After a literature review, a summary of studies that have analysed the association between BMI and mortality on patients who had a stroke is presented below.

The systematic approach used to conduct this literature review included the following inclusion criteria:

- type of studies and participants: observational prospective studies of human adults who had a stroke at baseline and a record of BMI obtained (as soon as possible) after the event
- outcome: mortality, assessed in different categories of BMI

This review excluded studies that looked at the incidence of stroke and mortality in a cohort of initially healthy individuals and studies that included participants who had a TIA.

In order to identify relevant studies, “Ovid Medline” and “Embase” electronic databases were searched (up to August 2013) and several search terms were used to define “stroke”, “body mass index” and “mortality”:

- stroke(s)
- post-stroke
- poststroke
- cerebrovascular accident
- cerebral infarction
- cerebral haemorrhage
- subarachnoid haemorrhage
- body mass index
- obese/ obesity / obesity paradox
- mortality/ survival

The full search strategy can be found in appendix 3.1. After removing the duplicates, 3774 references were found and only 8 studies were identified as being relevant for the analysis of the association between BMI and mortality after stroke (table 3.1).

Table 3.1 - Papers studying the associations between BMI and mortality in stroke populations

Year, author (country)	**Number of subjects, type of stroke, age**	**Follow-up period**	**Results: mortality hazard ratio comparing to the normal weight category**	**Results corrected for the possible confounders**	**Limitations and notes**
2003, FOOD Trial Collaboration (several countries)	3012 patients with undefined strokes	6 months	Underweight: 1.82 (1.34-2.47) Overweight: 0.87 (0.65-1.15)	Age, prestroke function, living conditions and stroke severity	Only 20% of patients were weighed or had their BMI calculated and there was a lack of standardization of assessment of nutritional status, with a large proportion of patients having their nutritional status assessed informally (i.e. based on simple observation, as a bedside assessment).
2008, Olsen et al (Denmark)	21884 ischaemic and haemorrhagic strokes (excluding subarachnoid haemorrhages and TIAs)	Up to 5 years (median: 1.5 years)	Underweight: 1.63 (1.41-1.90) Overweight: 0.73 (0.66-0.81) Obesity: 0.84 (0.74-0.96) Severe obesity: 0.84 (0.64-1.10)	Age, sex, civil status, SSS (severity of stroke scale) and risk factors. Obtained same result without risk factors.	Only patients over 40 years; BMI was measured in only 21884 patients (55%) and, from these, complete data set available for only 13242 patients (60%)
2009, Towfighi and Ovbiagele (United States of America)	644 ("majority of strokes in this study were likely ischaemic")	It varies (mean time: 14.1 years)	BMI increases were associated with: - lower mortality in the elderly - higher mortality in the younger individuals	Several risk factors for stroke	Sample size is inadequate; relies on self-reported history of stroke (data were obtained from a national survey); BMI was not assessed when patients had a stroke; all patients with BMI <25 kg/m^2 in a single category, with no separate analysis of underweight patients
2011, Vemmos et al (Greece)	2785, only first strokes, ischaemic and haemorrhagic strokes (excluding subarachnoid haemorrhages and TIAs)	Mean follow-up of 47 +/- 37 months (range, 1day-10years)	Overweight: 0.82 (0.71-0.94) Obesity: 0.71 (0.59-0.86)	Gender, stroke subtype, severity of stroke scale, age and risk factors	All patients with BMI <25 kg/m^2 in a single category, with no separate analysis of underweight patients; from the entire cohort of 2820 patients, 35 (1.2%) were excluded because of lack of data regarding body weight or height or both.

2011, Ryu et al (Republic of Korea)	1592 patients with ischaemic strokes	Median follow-up of 4 years (range, 1 – 2,693 days)	Underweight: 2.79 (1.92–4.05) Overweight: 0.95 (0.73–1.25) Obesity: 0.76 (0.57–1.01)	Age, sex, previous stroke, hypertension, diabetes, current smoking, heart disease and admission NIHSS score categorized into 0–1, 2–3, 4–6, and ≥7.	Patients whose height could not be obtained due to a severe neurological status during admission (n=36) were excluded. Included only ischaemic strokes. Cut-offs of BMI groups used in this study were based on WHO criteria for the Asian Pacific population
2011, Kim et al (33 stroke centers across Republic of Korea)	1604 patients with intracerebral haemorrhage	Mean follow-up of 33.6 +/- 15.5 months (no significant results were found at 30 days)	<18.5 Kg/m^2: 1.64 (1.11–2.40) 18.5–23 Kg/m^2: Reference 23.0–24.9 Kg/m^2: 0.69 (0.49–0.96) >25 Kg/m^2: 0.61 (0.43–0.88)	Age, diabetes, GCS score, glucose, volume of hematoma, and extension of haemorrhage into ventricles.	This study is a sub-analysis of an original study. From 1604 patients with an intracerebral haemorrhage, 248 (15.5%) were excluded due to lack of data or misclassification. Cut-offs of BMI groups used in this study were based on WHO criteria for the Asian Pacific population
2012, Kim et al (30 stroke centers across Republic of Korea)	34132, first and recurrent, ischaemic strokes	Mean follow-up of 32.6 +/- 23.1 months (no significant results were found at 30 and 90 days)	<18.5 Kg/m^2: 1.36 (1.25–1.48) 18.5–20 Kg/m^2: 1.14 (1.03–1.26) 20–23 Kg/m^2: Reference 23–25 Kg/m^2: 0.89 (0.84–0.95) 25–27.5 Kg/m^2: 0.82 (0.77–0.88) 27.5–30 Kg/m^2: 0.83 (0.74–0.92) 30–32.5 Kg/m^2: 0.77 (0.63–0.93) >32.5 Kg/m^2: 0.85 (0.64–1.12)	Data not available. However, in order to investigate the potential effect of age on risk of mortality, authors performed stratified analyses by age group.	This study is a sub-analysis of an original study. From 43723 registered acute stroke patients, 9591 (21.9%) were excluded by the pre-established selection criteria and, from the remaining 34132 patients, 5250 (15.4%) were excluded due to lack of BMI data. Cut-offs of BMI groups used in this study were based on WHO criteria for the Asian Pacific population
2013, Hassan et al (several hospitals across United States of America)	81579 patients with ischaemic strokes treated with intravenous thrombolysis	Until discharge from hospital	Non-obese: Reference Obese: 0.6 (0.5-0.8)	Age, sex, diabetes, hypertension, renal failure, hospital location and disease severity	These results were only related to in-hospital mortality, and the study was conducted in a subset of ischaemic strokes (only thrombolysed patients). The definition of “obese” and “non obese” is not provided.

BMI = body mass index

These results suggest a trend for an increased risk of mortality in the underweight patients and a decreased risk in overweight and/or obese patients.

When Towfighi and Ovbiagele (Towfighi and Ovbiagele, 2009) tried to assess the association between BMI and mortality among stroke survivors in continuous series of age, they found that in younger individuals an increase in BMI was marginally associated with a higher risk of mortality; but in the elderly, an increase in BMI was associated with a modest decrease in mortality (Towfighi and Ovbiagele, 2009). For example, an 80-year-old obese stroke survivor had a significant 42% lower risk of death than a normal-weight individual of the same age (HR 0.58, 95% CI 0.36 to 0.93) and an 80-year-old overweight individual had a non-significant reduced risk of death (by 20%) when compared with a normal-weight stroke survivor of the same age (HR 0.80, 95% CI 0.59 to 1.10). However, this study has major methodological limitations such as: the selection of the study participants was based on self-reported baseline history of stroke in non-institutionalized individuals from a national survey conducted between 1988 and 1994 (consequently, it was not possible to adjust for severity of stroke, there was no information regarding type of stroke and BMI was not assessed at the time that the individuals had a stroke); when BMI was analysed as categorical variable, normal and underweight people were grouped together into a "nonoverweight" group (BMI < 25Kg/m^2), which does not allow to determine the association between these 2 different BMI categories (normal and underweight, separately) and mortality.

In a prospective study of 2785 patients with ischaemic and haemorrhagic first-ever strokes conducted in Greece (Vemmos et al., 2011), BMI was assessed on admission to hospital in the acute phase post stroke, all data were entered into a stroke database, and the mean follow-up period was 47 months (up to 10 years). Only 1.2% of patients were excluded because of lack of BMI data but unfortunately, this study also grouped underweight and normal weight individuals into the same category "normal weight". It was observed that obese and overweight stroke patients had significantly better short (1 week and 1 month) and long-term survival (10 years) compared to those with normal BMI. In the multivariable analysis, after taking into consideration several potential confounders including stroke severity, HR of 10-mortality was 0.82 (95% CI 0.71 – 0.94) for the overweight group and 0.71 (95% CI 0.59 – 0.86) for the obese group, when compared with the "normal weight" group (Vemmos et al., 2011).

Similar results were obtained in a Danish cohort with 21884 patients (Olsen et al., 2008), as well as in two studies conducted in the Republic of Korea – one with ischaemic strokes (Ryu et al., 2011), the other with haemorrhagic strokes (Kim et al., 2011) – and in a multicenter observational study that included the first 3012 patients randomized in the FOOD trial (Dennis, 2003). All these four studies have also determined the risk of mortality of the underweight group of patients, which was significantly higher when compared with the "normal weight" group.

However, each of these studies had other limitations, as follows.

The Danish study is based on data collected for a registry started in 2001, which aims to capture all hospitalized ischemic and hemorrhagic stroke patients, aged 40 years or older, in Denmark. From all patients included in this registry, only 55% had their BMI assessed on admission to hospital, and from these, complete dataset was available for only 60%. Thus, multivariable analyses included 13242 first and recurrent strokes, with a follow-up period up to 5 years post stroke (mean of 1.5 years). After controlling for the effect of age, gender, civil status, severity of stroke and risk factors, risk of mortality was higher for underweight patients (HR 1.63, 95% CI 1.41–1.90) and lower for overweight, obese and severely obese individuals (HR 0.73, 95% CI 0.66–0.81; HR 0.84, 95% CI 0.73–0.98; HR 0.84, 95% CI 0.64–1.10, respectively), when compared with the normal weight group. Authors reported to have repeated the analyses without risk factors, and the effect of BMI on mortality remained the same (Olsen et al., 2008).

Similar results were found when the study population was limited to haemorrhagic strokes. In 2011, Kim and his colleagues analysed the association between BMI and mortality in 1365 haemorrhagic stroke patients recruited from 33 stroke centers across Republic of Korea. Over a mean follow-up period of 33.6 months, and after controlling for the effect of age, diabetes, severity of stroke, glucose, volume of haematoma and extension of haemorrhage into ventricles, there was an increased risk of death for underweight individuals (HR 1.64, 95% CI 1.11–2.40) and a lower risk for overweight (HR 0.69, 95% CI 0.49–0.96) and obese patients (HR 0.61, 95% CI 0.43–0.88), when compared with the normal weight group. It should be noted that this study is a sub-analysis of an original study; and from 1604 patients with an intracerebral haemorrhage, 248 (15.5%) were excluded due to lack of data (it is not specified if this included BMI data) or misclassification. Cut-offs of BMI groups used in this study were based on WHO criteria for the Asian Pacific population, therefore BMI ranges for normal weight is 18.5–23 Kg/m^2, for overweight is 23.0–24.9 Kg/m^2 and for obesity is >25 Kg/m^2.

The same author published another study in 2012, with a larger population of first and recurrent ischaemic strokes (Kim et al., 2012). Data were extracted from the Korean Stroke Register, which is a nationwide prospective multicentre hospital based register of acute ischaemic strokes, established in 1999. From 43723 registered acute stroke patients, 9591 (21.9%) were excluded by the pre-established selection criteria and, from the remaining 34132 patients, 5250 (15.4%) were excluded due to lack of BMI data. Thus, 28882 patients were divided into 8 categories of BMI (reference category is BMI between 20 and 23) and the adjusted HR over a mean follow-up period of 32.6 months were: 1.36 (CI 1.25-1.48) for BMI <18.5 Kg/m^2, 1.14 (CI 1.03-1.26) for BMI 18.5-20 Kg/m^2, 0.89 (CI 0.84-0.95) for BMI 23-25 Kg/m^2, 0.82 (CI 0.77-0.88) for BMI 25-27.5 Kg/m^2, 0.83 (CI 0.74-0.92) for BMI 27.5-30 Kg/m^2, 0.77 (CI 0.63-0.93) for BMI 30-32.5 Kg/m^2, 0.85 (CI 0.64-1.12) for BMI > 32.5 Kg/m^2. The paradoxical association between BMI and mortality remained preserved when authors performed stratified analysis by groups of age (<55, 55-65, 65-75, 75-85, >85 years) and by causes of death (cancer, vascular and other). However, it should be noted that this study is also limited by the fact that it is a sub-analysis of an original study.

Another cohort of ischemic strokes was identified in the same country (Ryu et al., 2011). This is a study that included 1592 patients consecutively admitted to a South Korean Hospital within 48h post stroke. Survival analyses over a mean follow-up period of 4 years were conducted using the normal weight category of BMI between 18.5 and 23 Kg/m^2 as the reference group (as defined by the WHO criteria for the Asian Pacific population) and several models were presented. In the model that adjusted for the effect for age, sex, previous stroke, hypertension, diabetes, current smoking, and heart disease, HR for the underweight group (BMI < 18.5 Kg/m^2) was 2.54 (95% CI 1.77–3.63), for the overweight group (BMI between 23.0 and 24.9 Kg/m^2) was 0.77 (95% CI 0.60–1.00) and for the obese group (BMI ≥25.0 Kg/m^2) was 0.59 (95% CI 0.45–0.78). In another model, the results were adjusted for the variables of the previous model plus admission NIHSS score categorized into 0–1, 2–3, 4–6, and ≥7: HR for the underweight group was 2.79 (95% CI 1.92–4.05), for the overweight group was 0.95 (95% CI 0.73–1.25) and for the obese group was 0.76 (95% CI 0.57–1.01). It should be noted that 36 patients were excluded because height could not be obtained due to a severe neurological status.

The FOOD trial was already described in the “Introduction” (chapter 1) as being an international multicenter randomized trial that aimed to evaluate various feeding policies on stroke patients (Dennis et al., 2006). A total of 5033 participants were enrolled between 1995 and 2003, and an observational study was conducted with the first 3012 patients to determine whether baseline nutritional status (mainly based on “bedside assessment”) was an independent predictor of 6-month outcome after stroke (Dennis, 2003). Researchers (randomising clinicians) categorized patients with a recent first ever or recurrent stroke into undernourished (9.3%), normal (74.3%) or overweight (16.4%), based on a bedside assessment or, when practical, a full assessment. After adjustment for age, pre-stroke function, living conditions and stroke severity, risk of mortality was 1.82 (95% CI 1.34-2.47) for the underweight group and 0.87 (95% CI 0.65-1.15) for the overweight. The main limitations of this study include being a sub-analysis of an original study (with specific inclusion criteria) and the methodology/quality of the data collection, given that only 20% of patients were weighed or had their BMI calculated and there was a lack of standardization of assessment of nutritional status, with a large proportion of patients (60%) having their nutritional status assessed informally (i.e. based on simple observation, as a bedside assessment).

Another study looking at a subset of patients with ischaemic strokes, i.e., those treated with intravenous thrombolysis, also found that obese patients had significantly lower in-hospital mortality, when compared with non-obese patients (Hassan et al., 2013). 81579 patients with ischaemic strokes and treated with intravenous thrombolysis, admitted to 1050 USA hospitals between 2002 and 2009, were included in this study and the follow-up period was until discharge from hospital. The definition of BMI groups used by the authors is not very clear in this paper, as they claim to have “identified obese patients using comorbidity files with secondary confirmation by the ICD-9-CM diagnosis codes of 278.0, 278.00, or 278.01 in the discharge record”. Thus, patients were classified into non-obese (reference category) and obese (accounting for only 6.3% of all patients). After adjusting for the effect of age, sex, diabetes, hypertension, renal failure, hospital location and a surrogate marker of disease severity, the risk of in-hospital mortality was 0.6 (95% CI 0.5-0.8) for obese individuals, possibly due to their decreased rates of intracerebral haemorrhage (4.5% in obese patients vs. 6.3% in non-obese patients, p=0.01). However, limitations of this study include the fact that these results were only related to in-hospital mortality, it was conducted in a subset of ischaemic strokes (only thrombolysed patients), and the definition of “obese” and “non obese” used in this study hinders the comparison with other studies that have used the traditional assessment of BMI to define obese (and non-obese) patients. It should be noted that only 6% of this study population was classified as obese, when compared with 24% of the other USA study discussed previously (Towfighi and Ovbiagele, 2009).

An additional small study also conducted in thrombolysed patients did not find significant differences between obese and lean patients in mortality at 90 days after stroke, but the authors of this conference abstract recognize the study was underpowered (Schlick et al., 2012).

However, all these studies present some limitations, which were partially identified above and will be further discussed at the end of this chapter.

After this literature review, it was possible to affirm that the available data regarding the associations between BMI and mortality after stroke over a long period of time were still limited, justifying the need for further investigations, especially in multi-ethnic populations, such as the population of London. None of the studies identified above have adjusted the results for the effect of ethnicity, possibly because the study populations were ethnically homogeneous. However, it should be noted that other authors have shown that ethnicity plays an important role in the prognosis of those who have suffered a stroke (Wolfe et al., 2005).

An ongoing population-based register, recording strokes that occurred in south London, was used as the source of data for this study, which was designed to explore the associations between BMI and mortality in patients who have had a first stroke.

3.2 - Aim and hypothesis

The aim of this study was to determine the association between BMI and mortality after a first stroke.

The main hypothesis was that there is a significant difference in the risk of mortality between patients in different BMI categories who had a first stroke, up to 8-years after the event, independent of several potential confounders such as age and ethnicity.

3.3 - Methods

3.3.1 - Study population

The South London Stroke Register (SLSR) is an ongoing population based stroke register recording first stroke in patients of all age groups, within a defined area of south London, and was set up in January 1995. Data are collected prospectively by the registry team, which is made up of doctors, nurses and research assistants/associates. Cases of stroke are identified, by using 12 referral sources, in the defined area that corresponds to 22 wards of Lambeth, Southwark, and Lewisham Health Commission (Stewart et al., 1999). At the 2001 Census, this multi-ethnic source population was composed of 271,817 individuals, with 63% white, 28% black and 9% of other ethnic groups (Crichton et al., 2012).

The referral sources are accident and emergency records; hospital wards; brain imaging requests; death certificates; coroner's records; general practitioners; hospital medical staff; community therapists; bereavement officers; hospital based stroke registries; general practice computer records; and "miscellaneous," including notification by patients or relatives of patients. Several methods are used to ensure complete ascertainment of cases (Stewart et al., 1999). Hence, for example, many patients who were not admitted to hospital when they had a stroke will attend a neurovascular clinic at the hospital and are registered there.

Hospital surveillance of admissions for stroke includes two teaching hospitals within and three outside the study area. Community surveillance of stroke includes patients under the care of all general practitioners within and on the borders of the study area (n=147).

Patients are examined and initial data are collected within 48 hours of notification to the register, when possible.

The complete initial form is filled in during the course of the hospital stay. The current version is divided into three sections. The first is completed as soon as possible after stroke and contains patient socio-demographic characteristics (e.g. age, ethnicity and living conditions prior to stroke), clinical assessment, risk factor history, stroke severity, etc. The next section is retained by the initialling team until the patient is discharged from hospital and bed/ward movements and other variables relating to inpatient care are collected along with discharge details and medications on discharge. The final part looks at stroke classification. Stroke is defined using WHO criteria and classified as cerebral infarction (ischaemic stroke), primary intracerebral haemorrhage and subarachnoid haemorrhage based on brain imaging (CT or MRI) within 30 days of stroke onset, necropsy examination, or cerebrospinal examination (for patients with subarachnoid haemorrhage). Where there is no known pathological confirmation of stroke subtype patients are classified as undefined (Crichton et al., 2012, Stewart et al., 1999).

This initial form is completed during the hospital stay and reviewed by clinicians. In summary, patients are assessed within 48hrs when possible but the process of completing the initial form takes place over the hospital stay.

Follow-up data are collected by a study nurse or specially trained field worker at 3 months, 12 months and then, annually after stroke, by postal questionnaire (Crichton et al., 2012).

The notification of death comes from the “Medical Research Information Service” (previously from the Office for National Statistics), based on NHS number of each patient or other characteristics, such as name, date of birth, place of last residence, etc.

It should be noted that information collected at initial assessment has been amended as practice has developed in response of results generated so far, such as BMI, which was included from 2004. Weight and height are clinical data obtained routinely and researchers (fieldworkers) collect this information if it is available in medical records. If these measurements are not recorded in medical notes, the researchers may register these data as “missing”, or may ask the patient or relative to recall them (but they never take the measurements themselves).

3.3.2 - Ethical considerations

Ethical approval (06/Q0702/147) for the SLSR and all research projects using register data was given by the Research Ethics Committees at Guy's and St Thomas' Hospitals and at King's College Hospital when the register commenced in 1995 and has regularly been renewed since.

Written informed consent needs to be obtained from all living patients before participation in the register. The patient must be allowed time to read the patient information booklet, before giving consent.

If a patient is not able to give consent, for example due to cognitive impairment, decreased consciousness, or expressive / receptive dysphasia, assent from the patient's carer or next of kin is taken instead.

3.3.3 - Study design and inclusion criteria

This is an analysis of a cohort of patients within the SLSR (observational prospective study).

Only patients who had a confirmed first stroke since 1st January 1995, and who were living in the study area at time of stroke were eligible to be included in the register.

Eligible patients must have been permanent residents in the area before the stroke happened. For people who just moved here, the expressly stated plan to make a permanent home in the study area is crucial.

It is aimed to register all patients prospectively within the first two weeks of their stroke and within 6 months at the latest. However, people with stroke will occasionally be registered retrospectively.

From this register, only data from patients who fulfilled the two key inclusion criteria were selected for the study of the association between BMI and mortality:

- registered on the SLSR with a record of BMI, and
- had a follow-up period of at least 1 year.

BMI has been included in the SLSR since 2004 and the official death records may take up to 6 months to arrive. In order to allow a minimum follow-up period of 1 year, this study included all patients admitted on the SLSR between 1st January 2004 and 31st of December 2010.

Data extraction was requested in July 2012, allowing for the minimum follow-up period of 1-year (i.e., mortality data were available up to December 2011) and for the maximum possible period of reception of mortality data (6 months).

3.3.4 - Data selection

a) baseline data

The following baseline data were extracted from the SLSR initial form:

- Patient identification number
- Date of stroke
- Date of admission
- Stroke subtype
- Age at time of stroke
- Ethnicity
- Living conditions prior to stroke
- Swallow test results (on admission to hospital)
- How weight was obtained
- Weight
- Height (this register does not include method used to obtain height)
- The NIHSS score (this score started to be collected only in the second half of 2004)
- Glasgow Coma Scale (GCS) score, a neurological scale that gives a reliable objective way of recording the conscious state of a person
- Risk factors diagnosed prior to stroke: hypertension, congestive cardiac failure (CCF), angina, myocardial infarction, TIA, migraine, atrial fibrillation, diabetes, depression, hypercholesterolaemia.

b) Mortality data

Mortality was the primary outcome and date of mortality (day/month/year), when available, was requested from January 2004 to December 2011.

3.3.5 - Statistical analysis

1. Patients were classified into 3 groups of BMI: less than 18.5 kg/m^2 (underweight), 18.5 to 24.9 kg/m^2 (normal weight) and 25.0 kg/m^2 or more (overweight). Further analyses were conducted with 4 groups, where the overweight group was divided into 25.0 to 29.9 kg/m^2 (overweight) and 30.0 kg/m^2 or more (obese).
2. Baseline characteristics of patient groups were compared using the Chi-square test for categorical variables and the ANOVA or the *t*-test for continuous variables.
3. To examine the effects of BMI on mortality during follow-up, Cox proportional hazards models were used to calculate crude and adjusted hazard ratios (HR) with 95% confidence intervals (CIs). The "normal weight" category was used as a reference. Multiple analyses were performed, e.g. with different types of stroke, and were adjusted for the several covariates, such as, age at time of stroke, gender, ethnicity, NIHSS score at admission, type of stroke. Further analyses were conducted with BMI as a continuous variable.

Data were analysed using SPSS software version 19.0 for Windows (Chicago**,** Illinois**,** USA). Any differences were considered statistically significant when $p < 0.05$.

3.4 - Results

All patients registered on the SLSR, from the 1st of January 2004 to the 31st of December 2010 were included in the analysis (n=1619 patients). Of these, 856 (53%) had records of weight and height, and therefore, BMI is available. For the remaining 763 (47%) individuals, no complete records (of weight, height or both parameters) existed.

As shown in figure 3.1, of those patients who had a record of BMI, the majority had ischaemic strokes, which is in line with national statistics, where the incidence of ischaemic strokes accounts for between 80 to 90% of all incident strokes (Bhatnagar et al., 2010).

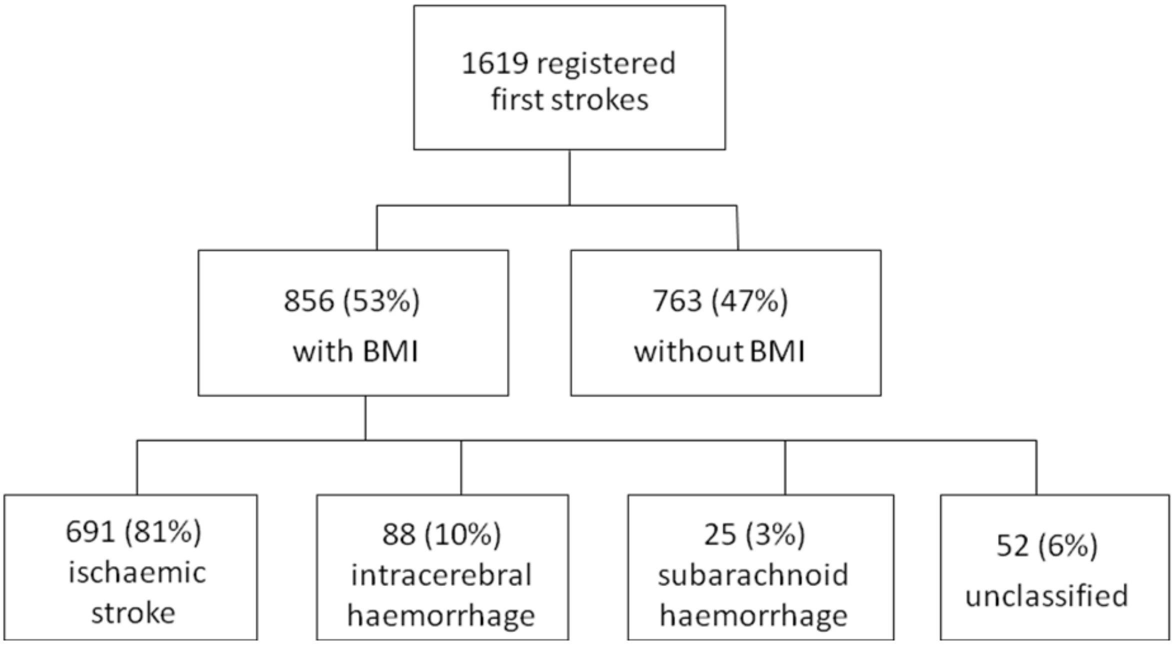


Fig. 3.1 - Number of patients included in the study, according to the availability of records of BMI and type of stroke

When comparing the group of patients with records of BMI with the group of patients with no records of BMI, there were no significant differences in type of stroke, gender and ethnicity. Rates of mortality at 1 month and at 8 years, mean age, mean NIHSS score and mean GCS score were significantly different between the groups. The group of patients with no records of BMI had a higher rate of mortality (3 times higher), was older, had a higher score of NIHSS and a lower score of GCS.

Higher scores of the NIHSS reflect more severe strokes and the lower the GCS score, the lower the patient's conscious state.

Table 3.2 - Baseline characteristics of patients with and without records of BMI.

	Group with BMI n=856	Group without BMI, n=763	*P* value
Type of stroke			0.108
Ischaemic, n (%)	691 (81)	580 (76)	
Haemorrhagic, n (%)	88 (10)	102 (13)	
Subarachnoid haemorrhage, n (%)	25 (3)	31 (4)	
Unclassified, n (%)	52 (6)	50 (7)	
Age, mean in years (SD)	68.5 (15.2)	70.2 (16.1)	0.031
Gender,			0.691
Male, n (%)	446 (52)	390 (51)	
Female, n (%)	410 (48)	373 (49)	
Ethnicity			0.098
White, n (%)	552 (65)	516 (71)	
Black Caribbean, n (%)	145 (17)	92 (13)	
Black African, n (%)	77 (9)	67 (9)	
Black other, n (%)	8 (1)	8 (1)	
Other, n (%)	65 (7)	48 (7)	
NIHSS score, mean (SD)	8.6 (7.5)	11.6 (10)	< 0.001
GCS score, mean (SD)	13.5 (2.9)	12.1 (4.1)	< 0.001
Rates of mortality at 1 month, n (%)	60 (7)	197 (26)	< 0.001
Rates of mortality at 8 years, n (%)	317 (37)	410 (54)	< 0.001

Numbers in parentheses indicate percentages for categorical data, which were tested with the Chi-squared test, and SD (standard deviation) for continuous data, which were tested with the Student's t-test.BMI = body mass index; NIHSS = National Institutes of Health Stroke Scale; GCS = Glasgow Coma Scale

The higher rate of mortality of the patients with no BMI recorded, in conjunction with the significantly higher mean NIHSS score, suggests that patients in this group were more likely to have severe strokes and die more quickly from that cause, i.e., patients did not have their BMI recorded probably due to their poor prognosis, and it could have been unsafe or unethical to weigh the patient.

For those patients with a record of BMI, the method used to obtain the weight was: measured for 416 (49%), recalled by patient or a relative for 293 (34%) and obtained from medical records for 147 (17%). The method used to obtain height was not described because this information is not collected.

Analyses were conducted in two different groups: a group with all types of strokes and a group with ischaemic strokes only. The last option removes the effect of heterogeneity relating to stroke subtype and enables comparison with previous studies conducted exclusively in ischaemic strokes.

All types of strokes

Patients were followed-up for a mean (survival) period of 1.3 +/-1.7 years.
The maximum possible period of follow-up (8 years) started on 1st of January 2004 and finished on 31st of December 2011.
Patients who had a stroke early in 2004 had a follow-up period of 8 years; those who had a stroke at the end of 2010 had a follow-up of 1 year. The following histogram shows the number of patients who had a stroke in each year, from 2004 to 2010.

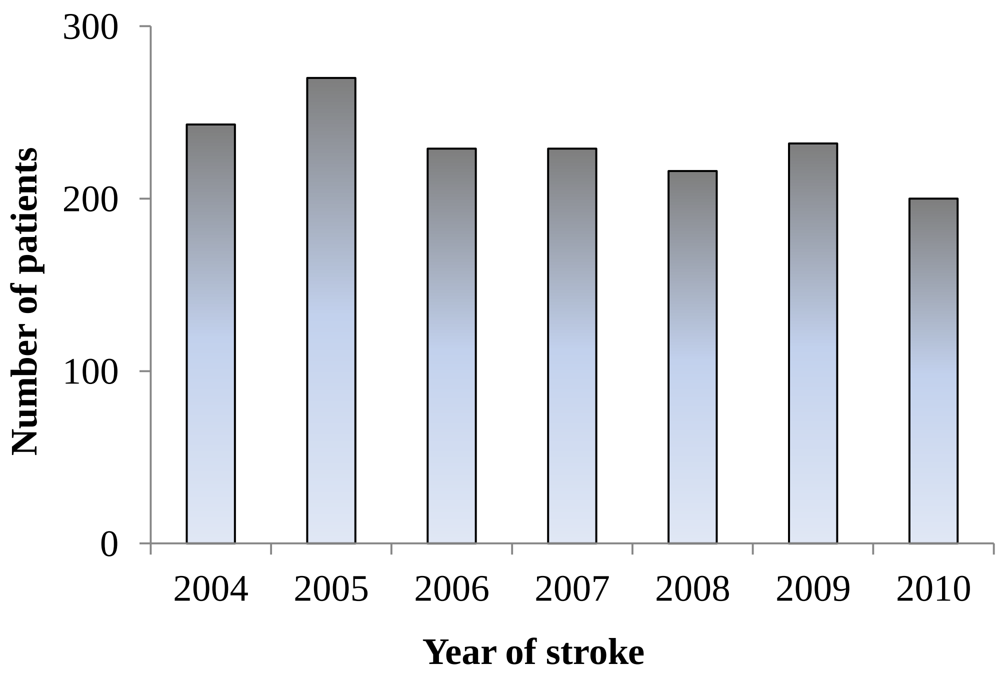


Fig. 3.2 - Number of patients who had a stroke in each year, from 2004 to 2010

For these 856 patients, mean age was 68.5 +/- 15 years (including individuals from 18 to 100 years old), 49 (6%) were underweight, 331 (39%) were normal weight and 476 (55%) were overweight (see figure 3.3). Of this overweight group, 24% (202) were obese (>30 kg/m^2).

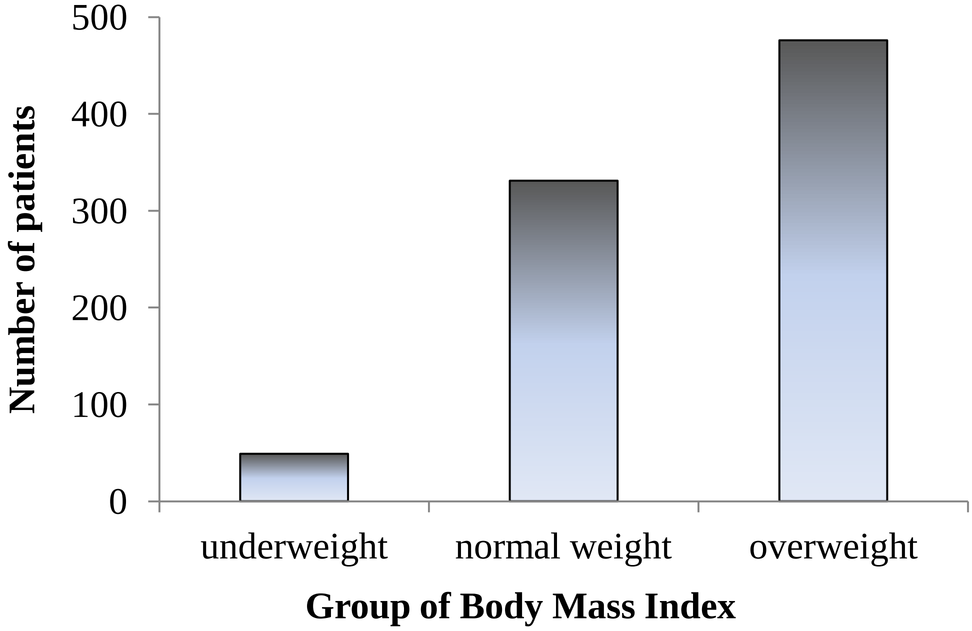


Fig. 3.3 - Number of patients (with all types of strokes) in each group of BMI

The following table (table 3.3) summarizes the baseline characteristics of the 3 groups of BMI.

Table 3.3 - Baseline characteristics of patients with all types of stroke, according to BMI groups.

	Underweight n=49 (6%)	Normal weight n=331 (39%)	Overweight n=476 (55%)	*P* value
Type of stroke				
Ischaemic, n (%)	40 (82)	264 (80)	387 (81)	0.002
Haemorrhagic, n (%)	5 (10)	34 (10)	49 (10)	
Subarachnoid haemorrhage, n (%)	2 (4)	19 (6)	4 (1)	
Unclassified, n (%)	2 (4)	14 (4)	36 (8)	
Age, mean in years (SD)	75.9 (12.9)	68.8 (17.3)	67.5 (13.6)	0.001
Range (minimum – maximum)	34-98	18-100	26-96	
Gender,				0.409
Male, n (%)	21 (43)	175 (53)	250 (53)	
Female, n (%)	28 (57)	156 (47)	226 (47)	
Ethnicity				0.018
White, n (%)	38 (78)	224 (69)	290 (61)	
Black Caribbean, n (%)	5 (10)	46 (14)	94 (20)	
Black African, n (%)	4 (8)	20 (6)	53 (11)	
Black other, n (%)	0 (0)	5 (1)	3 (1)	
Other, n (%)	2 (4)	31 (10)	32 (7)	
NIHSS score, mean (SD)	8.1 (5.9)	9.0 (8.1)	8.4 (7.1)	0.483
GCS score, mean (SD)	14.1 (1.8)	13.2 (3.3)	13.6 (2.7)	0.084
Living conditions prior to stroke				0.008
Home, n (%)	41 (84)	297 (89.7)	440 (93)	
Institutionalized, n (%)	6 (12)	33 (10)	27 (6)	
Other, n (%)	2 (4)	1 (0.3)	4 (1)	
Risk factors				
hypertension, n (%)	26 (54)	188 (57)	345 (73)	< 0.001
CCF, n (%)	3 (6)	12 (4)	18 (4)	0.680
angina, n (%)	4 (8)	27 (8)	63 (13)	0.063
myocardial infarction, n (%)	3 (6)	24 (7)	55 (11)	0.082
TIA, n (%)	3 (6)	41 (13)	49 (10)	0.371
migraine, n (%)	2 (4)	9 (3)	25 (3)	0.218
atrial fibrillation, n (%)	6 (13)	45 (14)	55 (12)	0.682
diabetes, n (%)	6 (12)	55 (17)	136 (29)	< 0.001
depression, n (%)	4 (9)	22 (9)	31 (8)	0.907
hypercholesterolaemia, n (%)	8 (17)	76 (23)	166 (35)	< 0.001

Numbers in parentheses indicate percentages for categorical data, which were tested with the Chi-squared test, and SD (standard deviation) for continuous data, which were tested with the ANOVA test.
BMI = body mass index; NIHSS = National Institutes of Health Stroke Scale; GCS = Glasgow Coma Scale; CCF = congestive cardiac failure; TIA = transient ischaemic attack.

There was a statistically significant difference between BMI categories regarding the type of stroke, ethnicity (more white patients in the underweight group and more black patients in the overweight group), age (underweight patients tended to be older) and living conditions (with more overweight patients coming from home and more underweight patients coming from an institution).

With regards to the risk factors, there was a statistically significant difference between BMI categories in the prevalence of hypertension, diabetes mellitus and hypercholesterolemia, all of which were higher in the overweight group.
Gender and severity of stroke were not significantly different between groups.

Kaplan Meier methods were used to estimate early (6 months) and long term (up to 8 years) survival across BMI categories and survival functions were compared using log rank tests (table 3.4 and figure 3.4).

Table 3.4 - Early and long term survival rates of patients who had a stroke, in each BMI category

	Survival rates at 6 months (%) (log rank test, *p=0.008*)	**Survival rates up to 8 years (%)** (log rank test, *p<0.001*)
Underweight	71.4	32.7
Normal weight	83.1	60.1
Overweight	87.2	68.1

Survival functions of three BMI groups were significantly different at both periods of time. Underweight patients had the lowest rates of survival, while overweight patients presented the highest rates of survival.

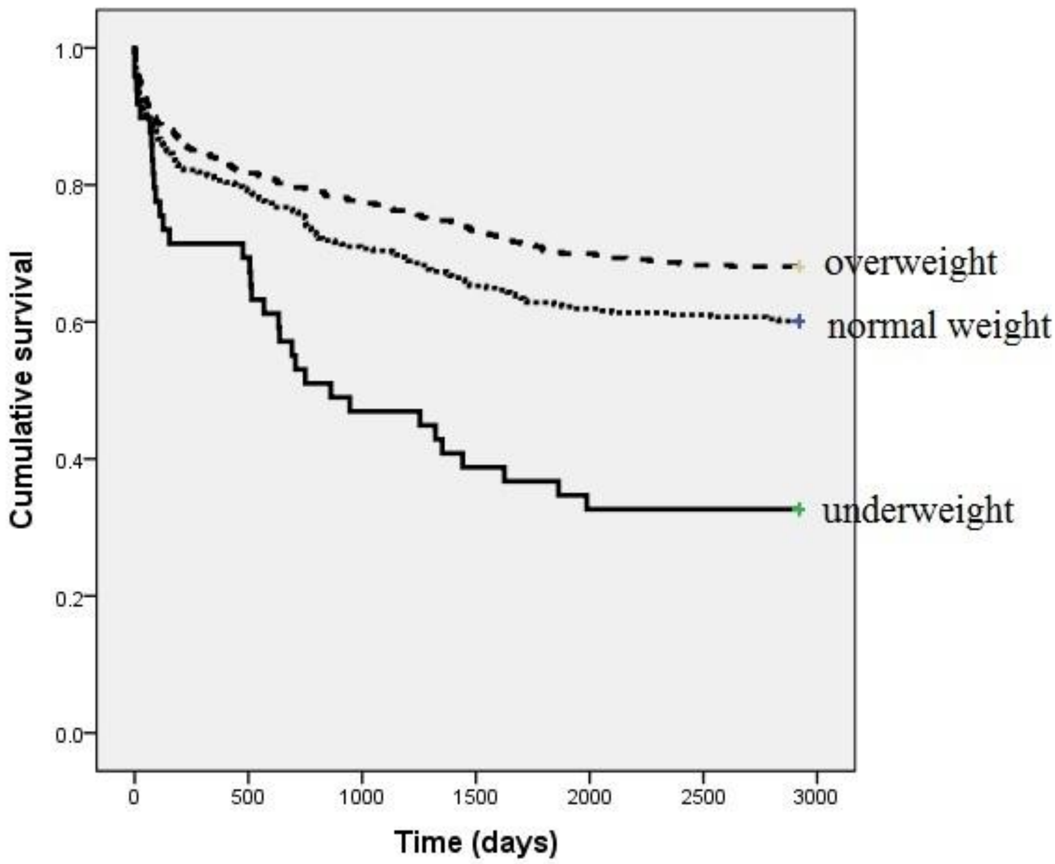


Fig. 3.4 - Long term survival (up to 8 years) of patients after stroke according to BMI group (log rank test, *p<0.001*)

Cox proportional hazards models were used to calculate crude and adjusted HR (hazard ratios), i.e. risk of mortality, with and without adjustment for possible confounders, over a period of 8 years.

Baseline characteristics presented in table 3.5 were included as covariates in the multivariable model, as all of them may have an influence on outcome (mortality).

"Normal weight" category was used as a reference and the results are summarized in the following tables and figures.

Table 3.5 - Risk of 8-year mortality according to BMI category, using univariate and multivariable Cox Proportional Hazards Models

BMI Category	**n (%)**	**Univariate Cox Proportional Hazards Model** (*p<0.001*)		**n (%)**	**Multivariable [a] Cox Proportional Hazards Model** (*p=0.009*)	
		HR	**95%CI**		**HR**	**95%CI**
Underweight	49 (6%)	2.10	1.43-3.07	48 (6%)	**1.82**	1.15-2.89
Normal weight	331 (38%)	Reference group		317 (38%)	Reference group	
Overweight	476 (56%)	0.76	0.60-0.86	463 (56%)	**0.89**	0.66-1.21

a *- results adjusted for the effect of type of stroke, ethnicity, age, gender, severity of stroke, living conditions prior to stroke, hypertension, CCF, angina, myocardial infarction, TIA, migraine, atrial fibrillation, diabetes, depression, hypercholesterolaemia.*
BMI = body mass index; HR = hazard ratio

There was a statistically significant difference in the risk of mortality between BMI categories, before *(p<0.001)* and after *(p=0.009)* adjusting for possible confounders. Having the normal weight category as a reference group, it was observed that the risk of mortality was higher for the underweight individuals (2.1 times and 82% more, in the crude and adjusted analyses, respectively) and lower for those who were obese (24% and 11% less, in the crude and adjusted analyses, respectively).

The multivariable analysis attenuated the relationship between BMI and post-stroke mortality in both underweight and overweight groups, which appeared to be largely due to the significant confounding effects of age *(p<0.001)*, NIHSS score *(p<0.001)*, atrial fibrillation (p=0.007) and diabetes mellitus *(p=0.043).*
Type of stroke *(p=0.964)*, gender *(p=0.099)*, living conditions *(p=0.677)*, ethnicity *(p=0.099)* and the remaining risk factors for stroke did not have a significant effect on this association (table 3.6).

Table 3.6 - Multivariable Cox Proportional Hazards Model showing the effect of different variables on 8-year mortality

	HR	**95% CI**	***p* value**
BMI groups			0.009
Underweight	1.82	1.15-2.89	
Normal weight (reference)	-----	-----	
Overweight	0.89	0.66-1.21	
Type of stroke			0.964
Ischaemic	Reference group	-	
Haemorrhagic	0.89	0.54-1.45	
Subarachnoid haemorrhage	1.09	0.33-3.54	
Unclassified	0.96	0.52-1.79	
Age (per 1-year increase)	1.06	1.05-1.08	<0.001
Ethnicity			0.099
White	Reference group	-	
Black Caribbean	0.69	0.45-1.08	
Black African	0.47	0.22-1.03	
Black other	0.71	0.17-2.92	
Other	0.54	0.28-1.06	
Gender (female)	0.79	0.59-1.05	0.099
NIHSS score (per 1-unit increase)	1.07	1.05-1.09	<0.001
Living conditions prior to stroke			0.677
Home	Reference group		
Institutionalized	1.04	0.67-1.63	
Other	0.42	0.57-3.06	
Risk factors			
Hypertension	0.92	0.64-1.21	0.631
CCF	1.59	0.85-2.99	0.162
Angina	0.79	0.49-1.28	0.351
Myocardial infarction	1.13	0.78-1.87	0.582
TIA	1.01	0.65-1.61	0.951
Migraine	0.51	0.13-2.19	0.351
Atrial fibrillation	1.61	1.15-2.31	0.007
Diabetes	1.44	1.02-2.03	0.043
Depression	1.09	0.60-1.97	0.769
Hypercholesterolaemia	0.72	0.53-1.02	0.051

BMI = body mass index; NIHSS = National Institutes of Health Stroke Scale; CCF = congestive cardiac failure; TIA = transient ischaemic attack; HR = hazard ratio.

This model included ethnicity divided into 5 groups and accounted for the importance of distinguishing black Caribbean from black African populations (while studying the impact of ethnicity on stroke risk factors (Hajat et al., 2004)). In view of the small numbers of patients within some groups of ethnicity, another model was run with ethnicity divided into 3 groups: white, black and other. The association between BMI and mortality remained the same (p=0.009) but ethnicity had a significant effect in this model (p=0.027) - see appendix 3.2.

Further analyses included the effect of smoking as a risk factor (see appendix 3.3), demonstrating that smoking has a significant effect on mortality *(p=0.026)* but does not affect the significant association between BMI and mortality *(p=0.017)*.

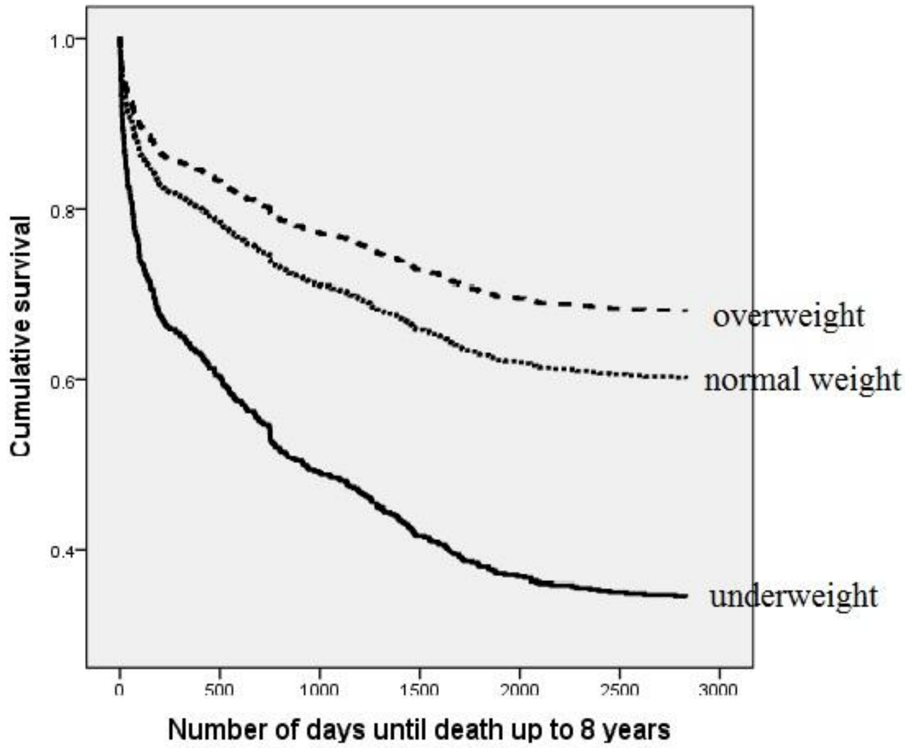


Fig. 3.5 - Cumulative survival after stroke according to BMI group (univariate analysis)

Not all patients had complete data for all covariates and, therefore, the number of patients included in this multivariable analysis (n=632) is lower than the number of patients included in the univariate analysis (n=856).

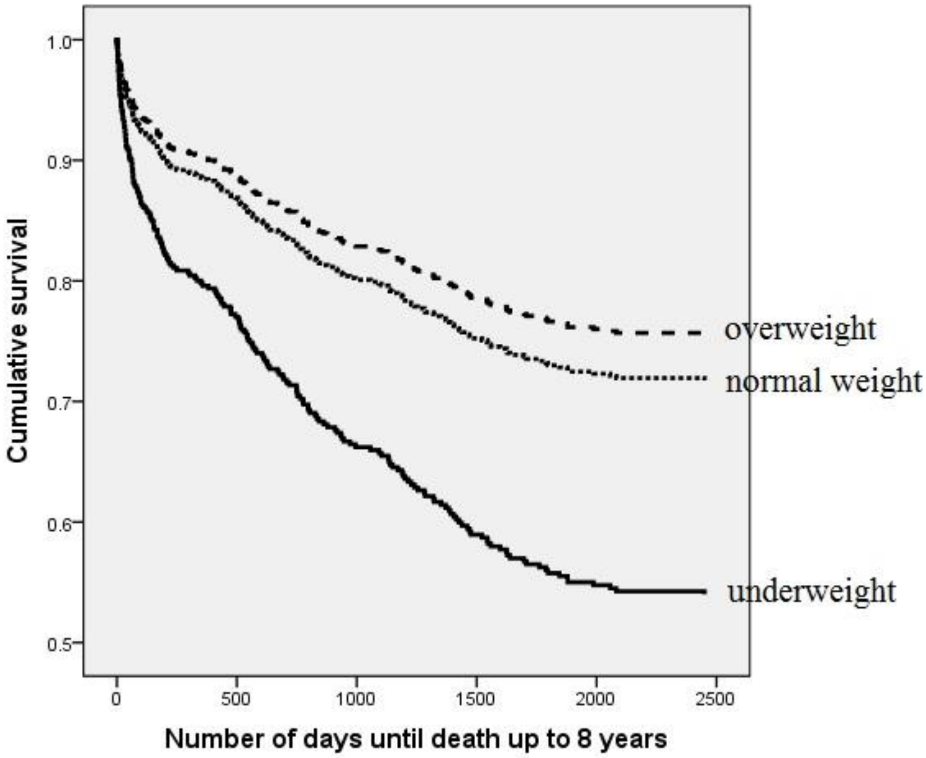


Fig. 3.6 - Cumulative survival after stroke according to BMI group (multivariable analysis)

While Kaplan-Meier survival curves show the proportion of patients alive at any point during the study with a series of horizontal steps of declining magnitude, Cox regression hazard functions produce continuous survival curves (assuming that the effect of the predictor variable(s) is constant over time). Although the Cox regression analysis allows taking into consideration the effect of other confounders, the log-rank test makes fewer assumptions and may be less prone to bias; hence both methods were used.

In order to know whether stroke risk factors influence the association between BMI and mortality, a multivariable Cox regression model was conducted, where results were adjusted for age, ethnicity, gender, living conditions, severity and type of stroke, but not for risk factors (hypertension, CCF, angina, myocardial infarction, TIA, migraine, atrial fibrillation, diabetes, depression, hypercholesterolaemia). Similar results were observed, i.e., there was a statistically significant difference in the risk of mortality across BMI categories *(p=0.003)*; when comparing to the normal BMI group, underweight patients had a significantly higher risk of mortality (HR, 1.82; 95% CI, 1.19-2.76) and overweight patients had a lower risk (HR, 0.87; 95% CI, 0.67-1.14).

It is noteworthy that this analysis without risk factors includes more individuals (n=721) than the analysis with risk factors (n=632), due to lack of information on risk factors for some patients (which may not be randomly distributed).

Hence, for this reason and because it was shown that risk factors do not affect the association between BMI and mortality, further multivariable analysis presented in this chapter (i.e. 4 categories of BMI, 2 groups of age, BMI as a continuous variable) did not include stroke risk factors.

Ischaemic strokes

The same statistical analyses were conducted for the subgroup of ischaemic strokes (n=691).

The follow-up period mentioned before was the same for this group of patients.

From the 691 patients included in this analysis, the mean age was 69.8 +/- 14 years (including individuals from 18 to 100 years old), 40 (6%) were underweight, 264 (38%) were normal weight and 387 (56%) were overweight. Of this overweight group, 166 (24%) were obese.

Similar to the analysis conducted on patients with all types of stroke, the following table (table 3.7) summarizes the baseline characteristics of the 3 groups of BMI of those individuals who had an ischaemic stroke.

Table 3.7 - Baseline characteristics of patients with ischaemic strokes, according to BMI groups.

	Underweight n=40	Normal weight n=264	Overweight n=387	*P* value
Age, mean in years (SD)	76.8 (12.3)	70.6 (16.2)	68.6 (13.1)	0.002
Range (minimum – maximum)	43-98	18-100	28-96	
Gender,				0.437
Male, n (%)	18 (45)	144 (55)	197 (52)	
Female, n (%)	22 (55)	120 (45)	332 (48)	
Ethnicity				0.078
White, n (%)	31 (78)	184 (70)	250 (65)	
Black Caribbean, n (%)	4 (10)	38 (15)	74 (19)	
Black African, n (%)	3 (7)	11 (4)	35 (9)	
Black other, n (%)	0 (0)	2 (1)	3 (1)	
Other, n (%)	2 (5)	26 (10)	22 (6)	
NIHSS score, mean (SD)	7.8 (5.9)	6.7 (7.4)	7.8 (6.6)	0.295
GCS score, mean (SD)	14.3 (1.4)	13.6 (2.9)	13.9 (2.4)	0.109
Living conditions prior to stroke				0.012
Home, n (%)	32 (80%)	238 (90%)	354 (92%)	
Institutionalized, n (%)	6 (15%)	25 (10%)	26 (7%)	
Other, n (%)	2 (5%)	1 (0.4%)	3 (1%)	
Risk factors				
hypertension, n (%)	21 (53)	158 (60)	282 (73)	0.001
CCF, n (%)	2 (5)	11 (4)	15 (4)	0.937
angina, n (%)	4 (10)	24 (9)	54 (14)	0.165
myocardial infarction, n (%)	3 (8)	21 (8)	46 (12)	0.213
TIA, n (%)	3 (8)	35 (13)	45 (12)	0.538
migraine, n (%)	2 (5)	5 (2)	22 (6)	0.065
atrial fibrillation, n (%)	6 (15)	42 (16)	48 (13)	0.410
diabetes, n (%)	4 (10)	45 (17)	111 (29)	< 0.001
depression, n (%)	4 (11)	17 (8)	28 (9)	0.860
hypercholesterolaemia, n (%)	8 (20)	66 (25)	139 (36)	0.004

Numbers in parentheses indicate percentages for categorical data, which were tested with the Chi-squared test, and SD (standard deviation) for continuous data, which were tested with the ANOVA test.
BMI = body mass index; NIHSS = National Institutes of Health Stroke Scale; GCS = Glasgow Coma Scale; CCF = congestive cardiac failure; TIA = transient ischaemic attack

Similar to the observations described for the group with all types of strokes, there was a statistically significant difference between BMI categories regarding age (being the underweight individuals those with a higher mean age) and living conditions (with a higher proportion of overweight patients coming from home and a higher proportion of underweight patients coming from an institution). With regards to the risk factors, there was also a statistically significant difference between BMI groups in the prevalence of hypertension, diabetes mellitus and hypercholesterolemia, which was higher in the overweight group and lower in underweight individuals.

The remaining risk factors, gender and severity of stroke were not significantly different between groups, as well as ethnicity (as opposed to what was observed in the group with all types of stroke).

Kaplan Meier methods were used to estimate early (6 months) and long term (up to 8 years) survival across BMI categories and survival functions were compared using log rank tests (table 3.8 and figure 3.7).

Table 3.8 - Early and long term survival rates of patients who had an ischaemic stroke, in each category of BMI

	Survival rates at 6 months (%) (log rank test, $p=0.002$)	**Survival rates up to 8 years (%)** (log rank test, $p<0.001$)
Underweight	70.0	32.5
Normal weight	83.0	57.2
Overweight	88.6	66.7

In this group of ischaemic strokes, survival functions of three BMI groups were also significantly different at both periods of time. Underweight patients had the lowest rates of survival, while overweight patients presented the highest rates of survival.

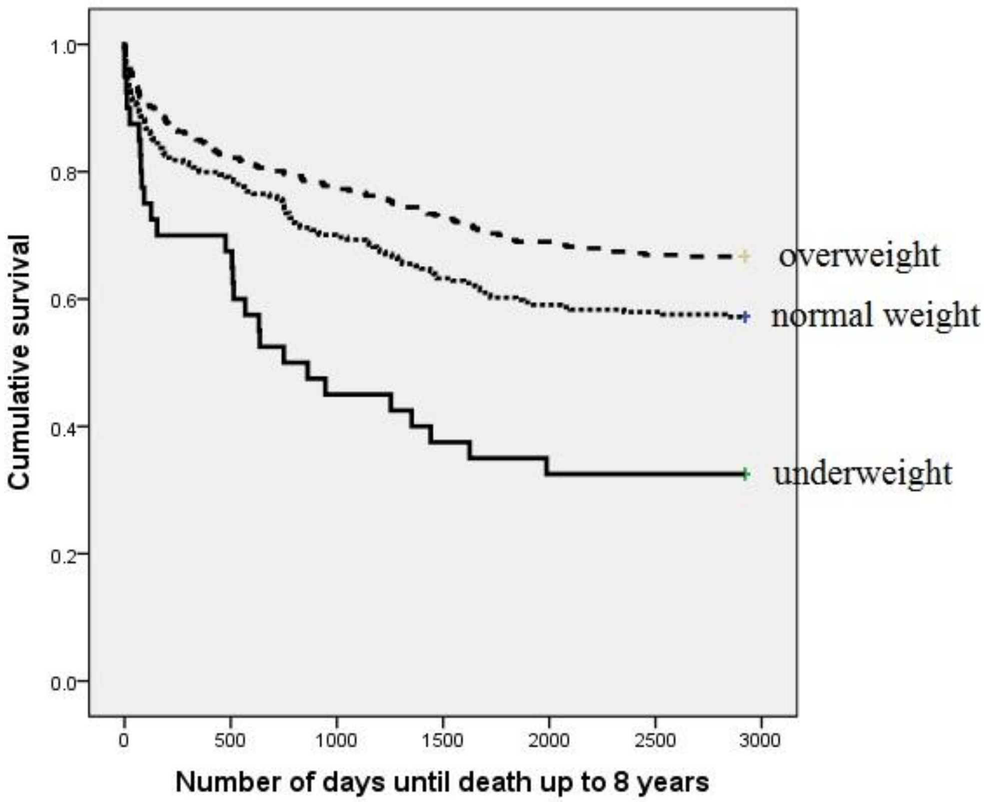


Fig. 3.7 - Long term survival (up to 8 years) of patients who had an ischaemic stroke, according to BMI group (log rank test, *p<0.001*)

Cox proportional hazards models were used to calculate crude and adjusted HR, i.e. risk of mortality, with and without adjustment for possible confounders, over a period of 8 years. Baseline characteristics presented in table 3.9 were included as covariates in the multivariable model, as all of them may have an influence on outcome (mortality).

"Normal weight" category was used as a reference and the results are summarized on the following tables and figures.

Table 3.9 - Risk of 8-year mortality according to BMI category, using univariate and multivariable Cox Proportional Hazards Models

BMI Category	**n (%)**	**Univariate Cox Proportional Hazards Model** (*p<0.001*)		**n (%)**	**Multivariable [a] Cox Proportional Hazards Model** (*p=0.011*)	
		HR	**95%CI**		**HR**	**95%CI**
Underweight	40 (6%)	2.02	1.32-3.07	32 (6%)	**1.81**	1.09-2.99
Normal weight	264 (38%)	Reference group		180 (35%)	Reference group	
Overweight	387 (56%)	0.72	0.56-0.93	300 (59%)	**0.84**	0.61-1.17

[a] - *results adjusted for the effect of age, gender, ethnicity, severity of stroke, living conditions prior to stroke, hypertension, CCF, angina, myocardial infarction, TIA, migraine, atrial fibrillation, diabetes, depression, hypercholesterolaemia.*
BMI = body mass index; HR = hazard ratio

There was a statistically significant difference in the risk of mortality across BMI categories, before *(p<0.001)* and after *(p=0.011)* adjusting for all possible confounders. Having the normal weight category as a reference group, it was observed that the risk of mortality was higher for the underweight individuals (2 times and 81% more, on the crude and adjusted analyses, respectively) and lower for those who were overweight (28% and 16% less (not significant), in the crude and adjusted analyses, respectively).

The multivariable analysis attenuated the relationship between BMI and post-stroke mortality in the overweight group, which appeared to be largely due to the significant confounding effects of age *(p<0.001)*, NIHSS score *(p<0.001)*, CCF *(p=0.042)*, atrial fibrillation (p=0.005), diabetes mellitus *(p=0.019)* and hypercholesterolaemia *(p=0.023).* Gender *(p=0.380)*, ethnicity *(p=0.174)*, living conditions *(p=0.853)* and the remaining risk factors for stroke did not have a significant effect on this association (table 3.10).

Table 3.10 - Multivariable Cox Proportional Hazards Model showing the effect of different variables on 8-year mortality

	HR	95% CI	*p* value
BMI groups			0.011
Underweight	1.81	1.09-2.99	
Normal weight (reference)	-----	-----	
Overweight	0.84	0.61-1.17	
Age (per 1-year increase)	1.06	1.05-1.08	<0.001
Ethnicity			0.174
White	Reference group	-	
Black Caribbean	0.73	0.46-1.16	
Black African	0.55	0.23-1.27	
Black other	0.46	0.62-3.41	
Other	0.49	0.23-1.05	
Gender (female)	0.87	0.64-1.19	0.380
NIHSS score (per 1-unit increase)	1.06	1.04-1.08	<0.001
Living conditions prior to stroke			0.853
Home	Reference group		
Institutionalized	1.04	0.64-1.68	
Other	0.58	0.08-4.29	
Risk factors			
Hypertension	0.96	0.67-1.36	0.804
CCF	2.12	1.03-4.31	0.042
Angina	0.75	0.45-1.25	0.268
Myocardial infarction	1.03	0.63-1.70	0.896
TIA	0.97	0.60-1.58	0.897
Migraine	0.61	0.15-2.52	0.498
Atrial fibrillation	1.70	1.18-2.46	0.005
Diabetes	1.59	1.08-2.33	0.019
Depression	1.03	0.54-1.96	0.940
Hypercholesterolaemia	0.66	0.47-0.96	0.023

BMI = body mass index; HR = hazard ratio; NIHSS = National Institutes of Health Stroke Scale; CCF = congestive cardiac failure; TIA = transient ischaemic attack.

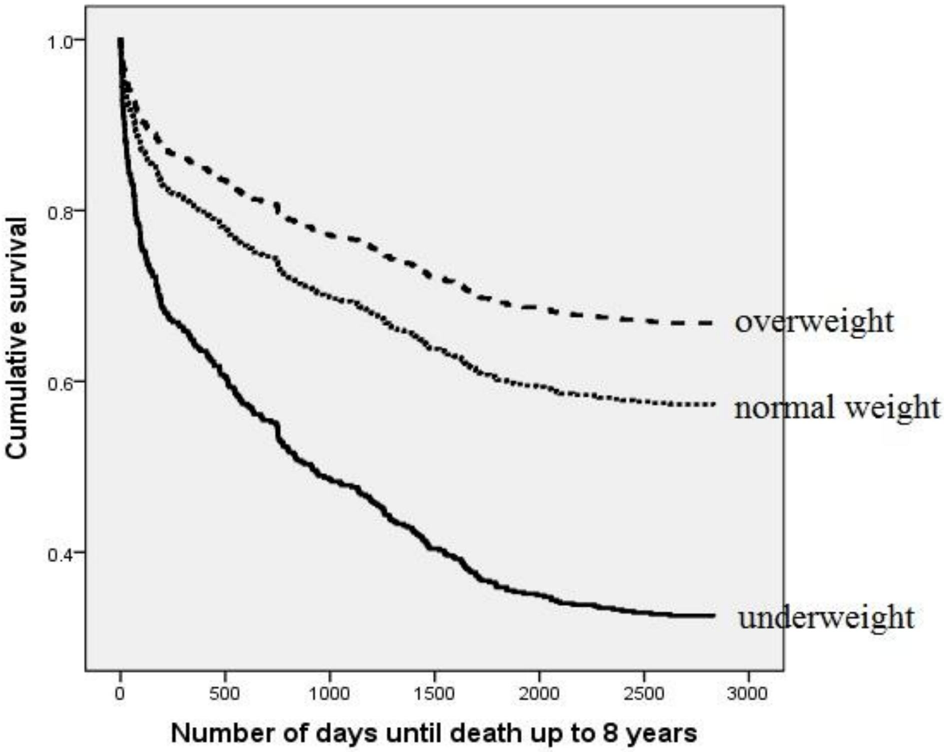


Fig. 3.8 - Cumulative survival after (ischaemic) stroke according to BMI group (univariate analysis)

Not all patients had complete data for all covariates and, therefore, the number of patients included in this multivariable analysis (n=512) is lower than the number of patients included in the univariate analysis (n=691).

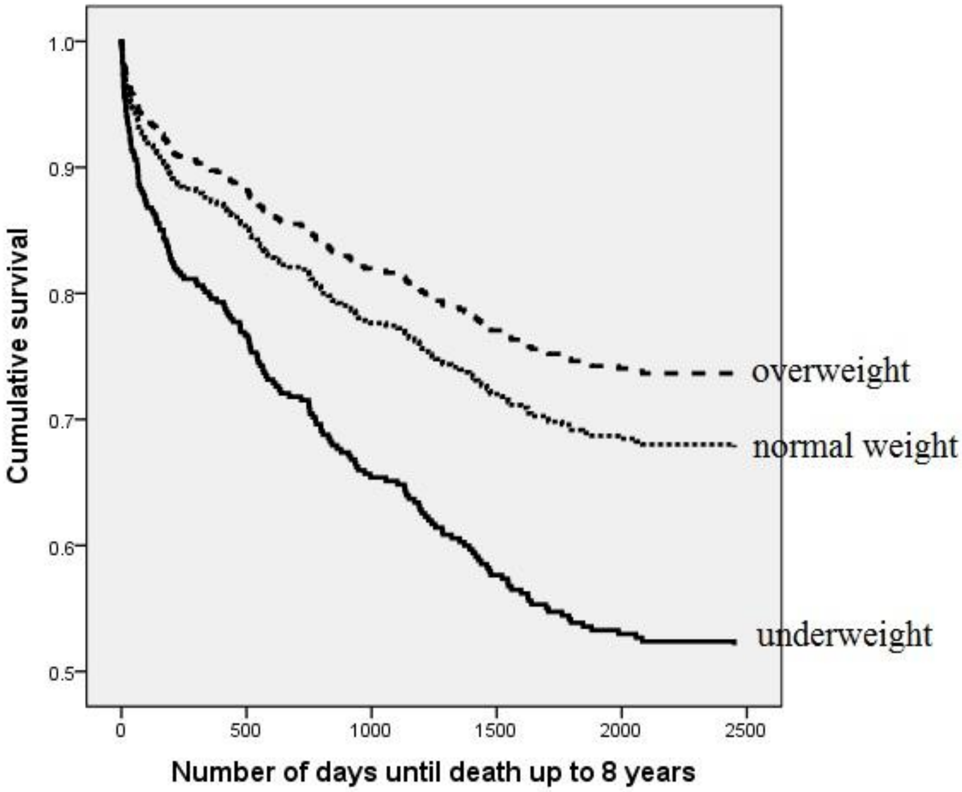


Fig. 3.9 - Cumulative survival after (ischaemic) stroke according to BMI group (multivariable analysis)

All types of strokes, 4 categories of BMI

Similar results were obtained when further analyses were conducted with the group of all types of strokes, dividing individuals into 4 categories of BMI. Thus, the previous overweight group (BMI>25Kg/m^2) was divided into 2 groups: overweight (BMI 25-29.9 kg/m^2) and obesity (BMI>30 kg/m^2).

The summary of the results is presented in table 3.11.

Table 3.11 - Survival rates and risk of 8-year mortality according to BMI category, using univariate and multivariable Cox Proportional Hazards Models

BMI Category	**n (%)**	**Survival rates (*p<0.001*, log rank test)**	**Univariate Cox Proportional Hazards Model** (*p<0.001*)		**Multivariable [a] Cox Proportional Hazards Model** (*p=0.006*)	
			HR	**95%CI**	**HR**	**95%CI**
Underweight	49 (6%)	33%	2.09	1.43-3.07	1.83	1.20-2.78
Normal weight	331 (38%)	60%	Reference group		Reference group	
Overweight	274 (32%)	65%	0.84	0.65-1.09	0.82	0.61-1.11
Obesity	202 (24%)	72%	0.65	0.48-0.89	0.96	0.68-1.37

a *- results adjusted for the effect of type of stroke, ethnicity, age, gender, ethnicity, severity of stroke and living conditions prior to stroke.*
BMI = body mass index; HR = hazard ratio

Rates of survival increased as BMI increased and the difference was statistically significant across BMI groups *(log rank test, p<0.001)*. Obese patients had the highest rate of survival over a period of 8 years (72%).

There was a statistically significant difference in the risk of mortality across BMI categories, before *(p<0.001)* and after *(p=0.006)* adjusting for possible confounders. Having the normal weight category as a reference group, it was observed that the risk of mortality was higher for the underweight individuals and lower for those who were overweight and obese.
However, the multivariable analysis attenuated the relationship between BMI and post-stroke mortality in the overweight and obese groups, to the extent that it was no longer statistically significant.

Not all patients had complete data for all covariates and, therefore, the number of patients included in this multivariable analysis (n=721) was lower than the number of patients included in the univariate analysis (n=856).

For the purpose of this thesis and given the relatively small sample size of this study, further analyses were conducted with 3 groups of BMI.

All types of strokes, 2 groups of age: over and under 65 years

It has been suggested that the association between BMI and mortality is age-dependent (Towfighi and Ovbiagele, 2009). Therefore, the group with all types of strokes (n=856) was divided in 2 groups of age (over and under 65 years); log rank tests, as well as univariate and multivariable survival analyses were conducted in each group. This cut-point is based on the definition of "elderly" or older person that is used in most developed world countries, including the UK (Age UK, 2013).
The younger group was composed of 309 individuals (36%) and the older of 547 (64%). Results are presented on the following tables, 3.11 and 3.12.

Table 3.12 - Survival rates and risk of 8-year mortality of patients aged under 65 years who had a stroke, according to BMI category, using univariate and multivariable Cox Proportional Hazards Models

BMI Category	**n (%)**	**Survival rates (*p=0.006*, log rank test)**	**Univariate Cox Proportional Hazards Model** (*p=0.017*)		**Multivariable [a] Cox Proportional Hazards Model** (*p=0.008*)	
			HR	**95%CI**	**HR**	**95%CI**
Underweight	6 (2%)	50.0%	4.14	1.20-14.2	4.68	1.25-17.26
Normal weight	117 (38%)	84.2%	Reference group		Reference group	
Overweight	186 (60%)	90.4%	0.70	0.36-1.37	0.58	0.26-1.32

[a] *- results adjusted for the effect of type of stroke, ethnicity, age, gender, ethnicity, severity of stroke and living conditions prior to stroke. BMI = body mass index; HR = hazard ratio*

Table 3.13 - Survival rates and risk of 8-year mortality of patients aged 65 and over who had a stroke, according to BMI category, using univariate and multivariable Cox Proportional Hazards Models

BMI/ Category	**n (%)**	**Survival rates (*p=0.005*, log rank test)**	**Univariate Cox Proportional Hazards Model** (*p=0.004*)		**Multivariable [a] Cox Proportional Hazards Model** (*p=0.029*)	
			HR	**95%CI**	**HR**	**95%CI**
Underweight	43 (8%)	30.2%	1.50	1.01-2.24	1.63	1.04-2.54
Normal weight	214 (39%)	46.4%	Reference group		Reference group	
Overweight	290 (53%)	53.6%	0.79	0.62-1.01	0.89	0.68-1.19

[a] *- results adjusted for the effect of type of stroke, ethnicity, age, gender, ethnicity, severity of stroke and living conditions prior to stroke. BMI = body mass index; HR = hazard ratio*

There was a statistically significant difference in survival rates between the 3 BMI categories, for both the over and under 65 years groups (log rank test, *p=0.006* and *p=0.005,* respectively) with lowest survival rates observed in the underweight categories and greater survival rates on the overweight categories.

Based on Cox regression models, the difference in risk of mortality across BMI categories was also statistically significant in both younger and older patients, before *(p=0.017* and *0.004,* respectively*)* and after *(p=0.008* and *0.029*, respectively*)* adjusting for possible confounders.

In both univariate and multivariable analyses and having the normal weight category as a reference group, the risk of mortality was higher for the underweight individuals and there was a non-significant trend for a lower risk of death in those who were overweight.

However, these results should be interpreted with caution due to the relatively small sample size of each group.
The group of patients under the age of 65 years old was composed of 309 individuals in the univariate analysis, and only 260 in the multivariable analysis (not all patients had complete data for all covariates, as explained before).
The group of patients aged 65 years and older had 547 subjects in the univariate analysis, and 461 in the multivariable analysis.

Mortality curves for both age groups, adjusted for the effect of type of stroke, ethnicity, age, gender, ethnicity, severity of stroke and living conditions prior to stroke, are shown on the following figures.

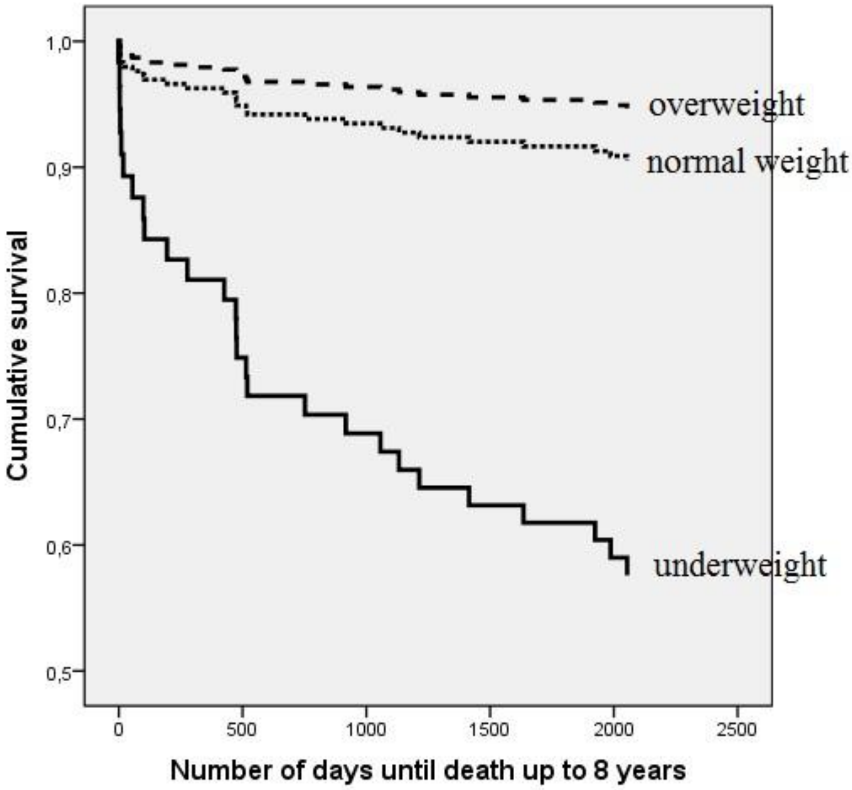


Fig. 3.10 - Cumulative survival of patients aged under 65, after a stroke, according to BMI group (multivariable analysis)

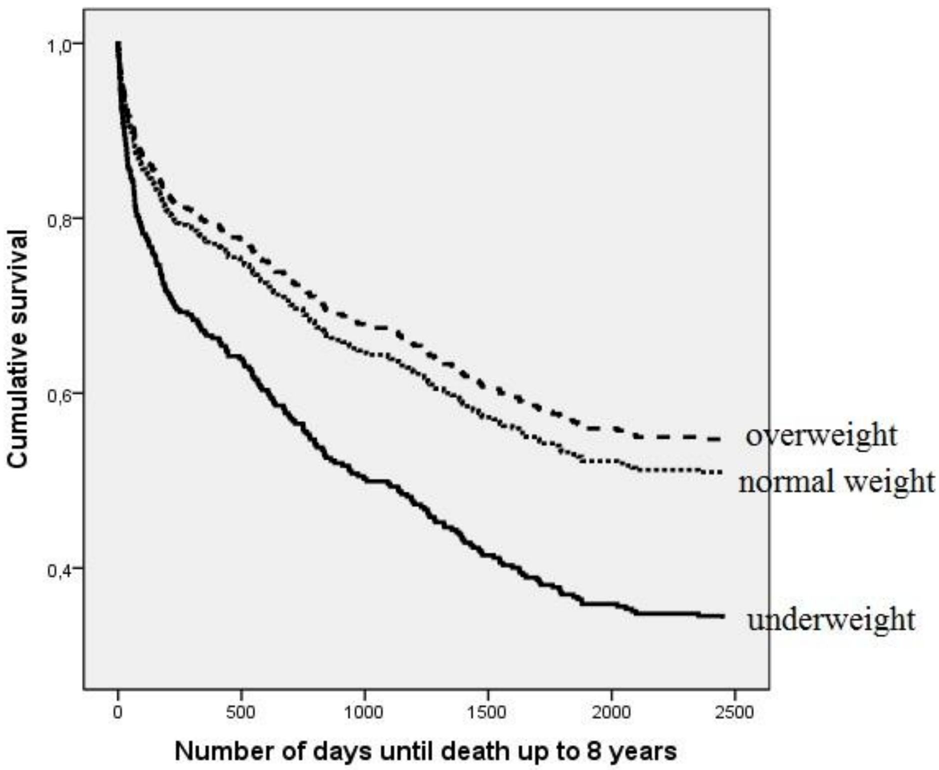


Fig. 3.11 - Cumulative survival of patients aged 65 and over, after a stroke, according to BMI group (multivariable analysis)

Analyses in different groups of ethnicity

It was demonstrated in the “Introduction” of this thesis that ethnicity plays an important role in the epidemiology of stroke, and on table 3.3, the distribution of patients according to ethnicity in each category of BMI was statistically significant (p=0.018). There was a higher proportion of white patients in the underweight group and a higher proportion of black (Caribbean and African) patients in the overweight group.

Analyses were not conducted separately in the black and white populations because the size of the black population is too small: the total number of black (Caribbean, African and other) patients is 230 or 194 and there are only 9 or 8 black patients in the underweight category in the univariate and multivariable analyses, respectively).

However, it should be noted that all the multivariable analyses presented in this section have been adjusted for the effect of ethnicity.

Survival analysis using BMI as a continuous variable

The analysis of BMI as a continuous variable allows the study of association between the entire distribution of the BMI and mortality, without losing the information imposed when BMI is grouped into categories. It also permits the identification of the level associated with a minimum risk of death. Hence, it was investigated whether the relationship between BMI and mortality is linear, quadratic or of a higher power.

Multivariable Cox regression models were performed using BMI as a continuous variable and taking in consideration the effect of age, ethnicity, severity of stroke, gender and type of stroke – table 3.14.

Table 3.14 - Multivariable Cox regression model output for 8-year mortality, using BMI as a continuous variable (linear and quadratic terms)

	Beta coefficient	**SE**	**HR (95% CI)**	***p* value**
BMI	-0.165	0.043	0.85 (0.78-0.92)	<0.001
BMI squared	0.002	0.001	1.002 (1.001-1.004)	<0.001
Type of stroke	-0.083	0.092	0.92 (0.78-1.10)	0.364
Gender	-0.214	0.193	0.81 (0.63-1.04)	0.100
NIHSS score	0.068	0.008	1.07 (1.05-1.09)	<0.001
Age	0.065	0.006	1.07 (1.05-1.08)	<0.001
Ethnicity	-0.158	0.073	0.85 (0.74-0.98)	0.030

After the adjustment for possible confounders, the quadratic term (BMI squared) was shown to be significant (*p<0.001*) on the model, which suggests that there is a U shaped relationship between BMI and mortality after stroke.

BMI was also fitted to the model as a cubic term, but the result was not significant *(p=0.522).*

The linear term is negative (Beta coefficient = -0.165) and the quadratic term (Beta coefficient = 0.002) is positive.

The graphed relationship was obtained by using the equation

$Y = \exp(\text{Beta}_{BMIsquared} \times BMI^2 + \text{Beta}_{BMI} \times BMI)$

and is presented in the figure 3.12.

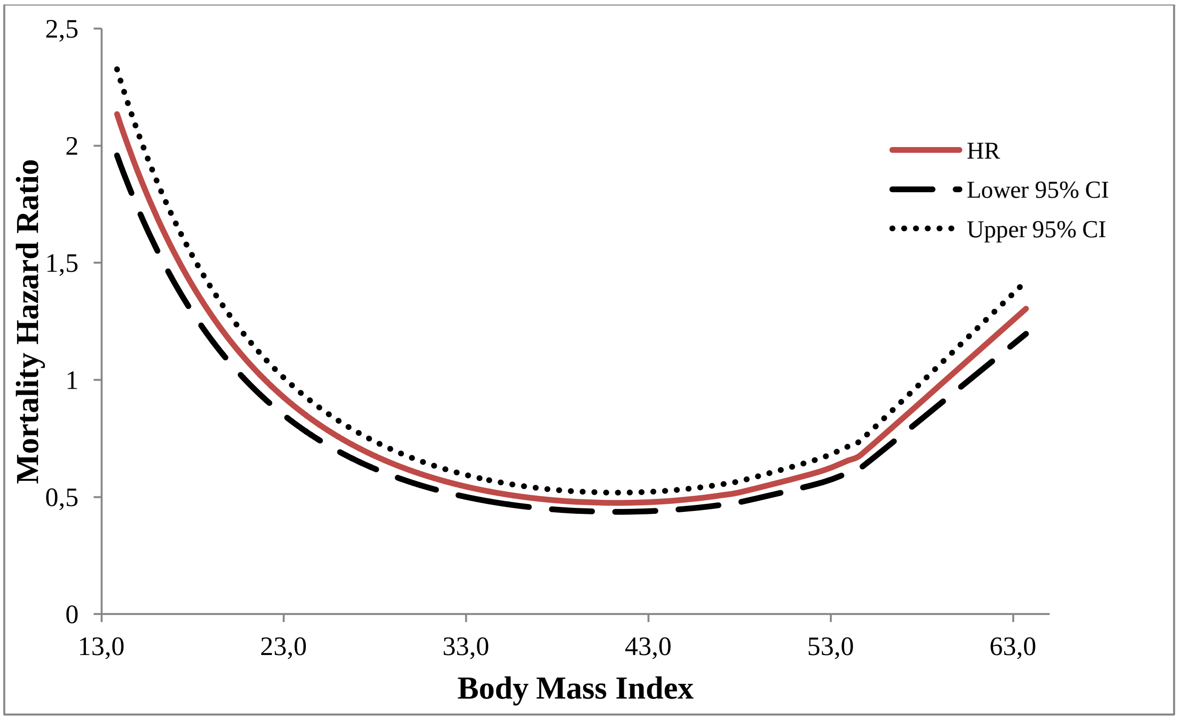


Fig. 3.12 - Adjusted 8-year mortality hazards ratio by BMI, showing the shape of the BMI-mortality association after a stroke

This curve shows an increased risk of death in the lowest BMI range and a modest elevation in risk of death in the highest range of BMI (>50 Kg/m^2). The lowest risk of mortality is located in the overweight group, when BMI = 41 Kg/m^2.

Knowing that a small proportion of outliers may affect the shape of the previous curve, a dot plot was created to identify data values that did not fit the trend of the data. This was the case for the 4 individuals with the highest values of BMI (BMI>50Kg/m^2, n=4) – fig. 3.13.

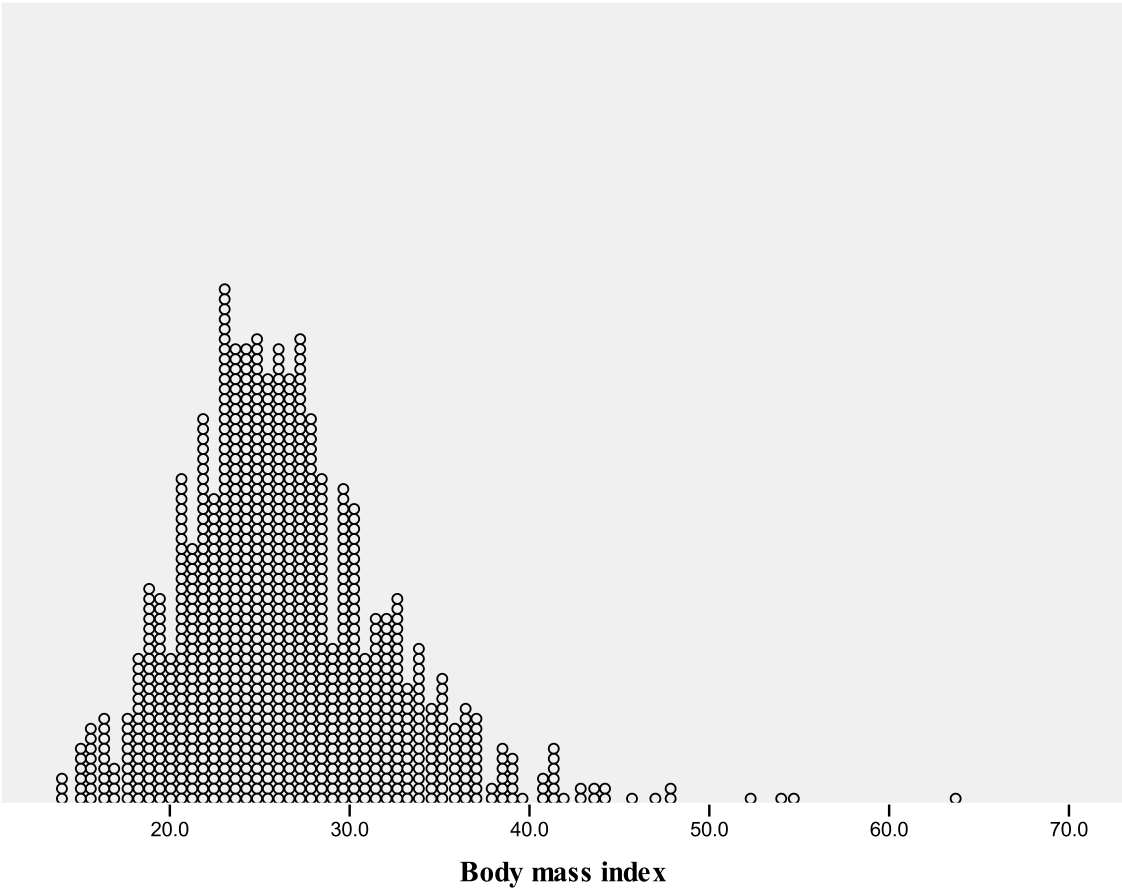


Fig. 3.13- Dot plot showing distribution of patients according to BMI

A model fit to the data when the 4 outliers were removed was conducted and results are shown on table 3.15.

Table 3.15 - Multivariable Cox regression model output for 8-year mortality, using BMI as a continuous variable (linear and quadratic terms), after removing outliers

	Beta coefficient	**SE**	**HR (95% CI)**	***p* value**
BMI	-0.198	0.074	0.82 (0.71-0.95)	<0.007
BMI squared	0.003	0.001	1.002 (1.000-1.006)	0.020
Type of stroke	-0.091	0.092	0.913 (0.76-1.10)	0.327
Gender	-0.226	0.132	0.79 (0.62-1.03)	0.087
NIHSS score	0.068	0.008	1.07 (1.05-1.09)	<0.001
Age	0.065	0.006	1.07 (1.06-1.08)	<0.001
Ethnicity	-0.157	0.073	0.86 (0.74-0.99)	0.032

After the adjustment for possible confounders, the quadratic term (BMI squared) was also shown to be significant (*p=0.02*) in the model, but not the cubic term (*p=0.104*). This equally suggests that there is a U shaped relationship between BMI and mortality after stroke.

The graphed relationship was obtained by using the equation $Y = exp\ (0.003\ x\ BMI^2 - 0.198\ x\ BMI)$ and is presented on the following figure.

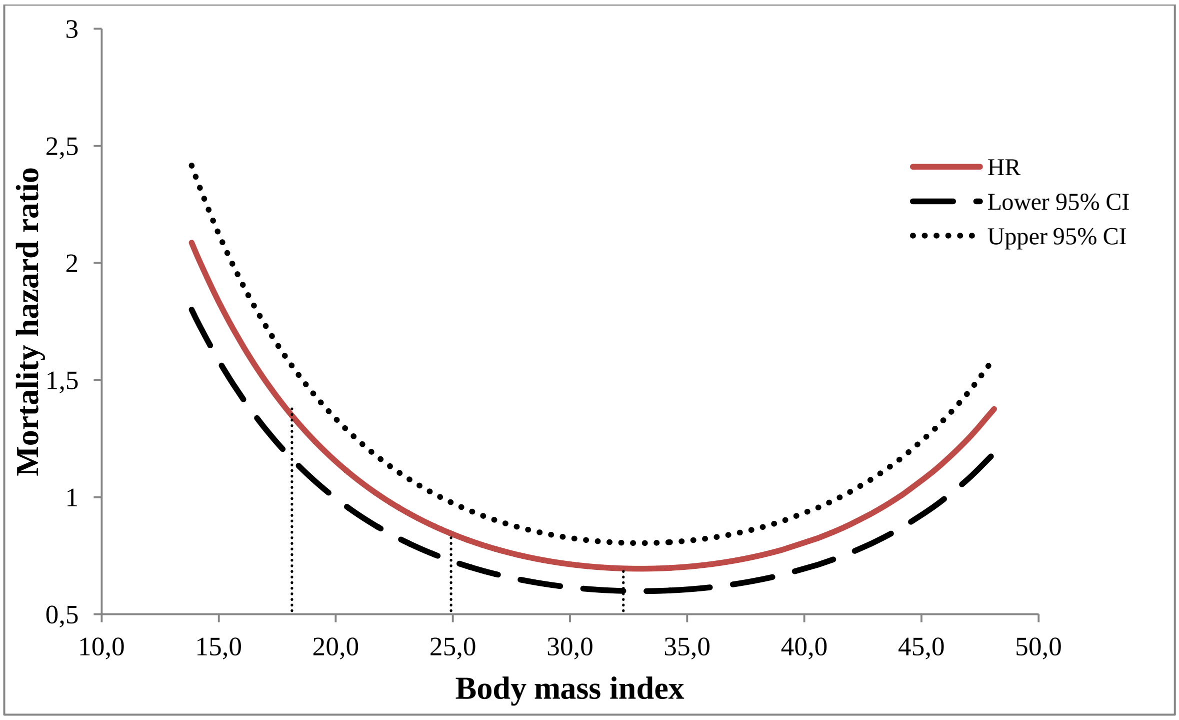


Fig. 3.14 - Adjusted 8-year mortality hazards ratio by BMI, showing the shape of the BMI-mortality association after a stroke. Extreme values of BMI (>50Kg/m^2) were excluded.

The laterally inverted J shaped curve did not change significantly after the removal of the 4 cases with extreme BMI values. The lowest risk of death continued to be located in the overweight group, when BMI = 33 Kg/m^2, as opposed to the findings of studies conducted in healthy populations, where all-cause mortality is generally lowest with a BMI of 20 to 25 Kg/m^2 (Berrington de Gonzalez et al., 2010) (see figure 3.15).

Barrington de Gonzalez and her colleagues pooled the data from 19 prospective studies that included 1.46 million non-Hispanic white adults, from 19-84 years old (median 58), which had a median follow-up period of 10 years (minimum of 5 years). Data came from prospective studies in the National Cancer Institute Cohort Consortium (involving more than 15 countries), where information on self-reported BMI at baseline, smoking status and pre-existing conditions (like cancer and heart disease) were available (Berrington de Gonzalez et al., 2010).

Fig. 3.15 was divided into men and women, and within each gender, there are 2 curves:

- "all subjects": includes all subjects, encompassing current of former smokers, and those who reported having cancer or heart disease at baseline
- "healthy subjects who never smoked": this group includes only individuals who reported no history of cancer or heart disease at baseline and who had never smoked. Thus, in this subgroup, results should not be affected by the confounding effect of smoking or prevalent illness. Also, the HR of both curves took into consideration the effect of age, alcohol intake, educational level, marital status and overall physical activity.

The authors of this study showed that all-cause mortality was generally lowest with a BMI between 20 and 25, and from 25 to 45 the higher the BMI, the higher the risk of death (particularly in healthy subjects who never smoked).

In summary, when figures 3.14 and 3.15 are compared, it is possible to see that the BMI-mortality curves are different between the healthy population (fig. 3.15, specially the healthy subjects who never smoked) and the stroke population (fig. 3.14). This reinforces the idea that the ideal BMI for the healthy population may be different from the ideal BMI for populations with some established diseases, like stroke.

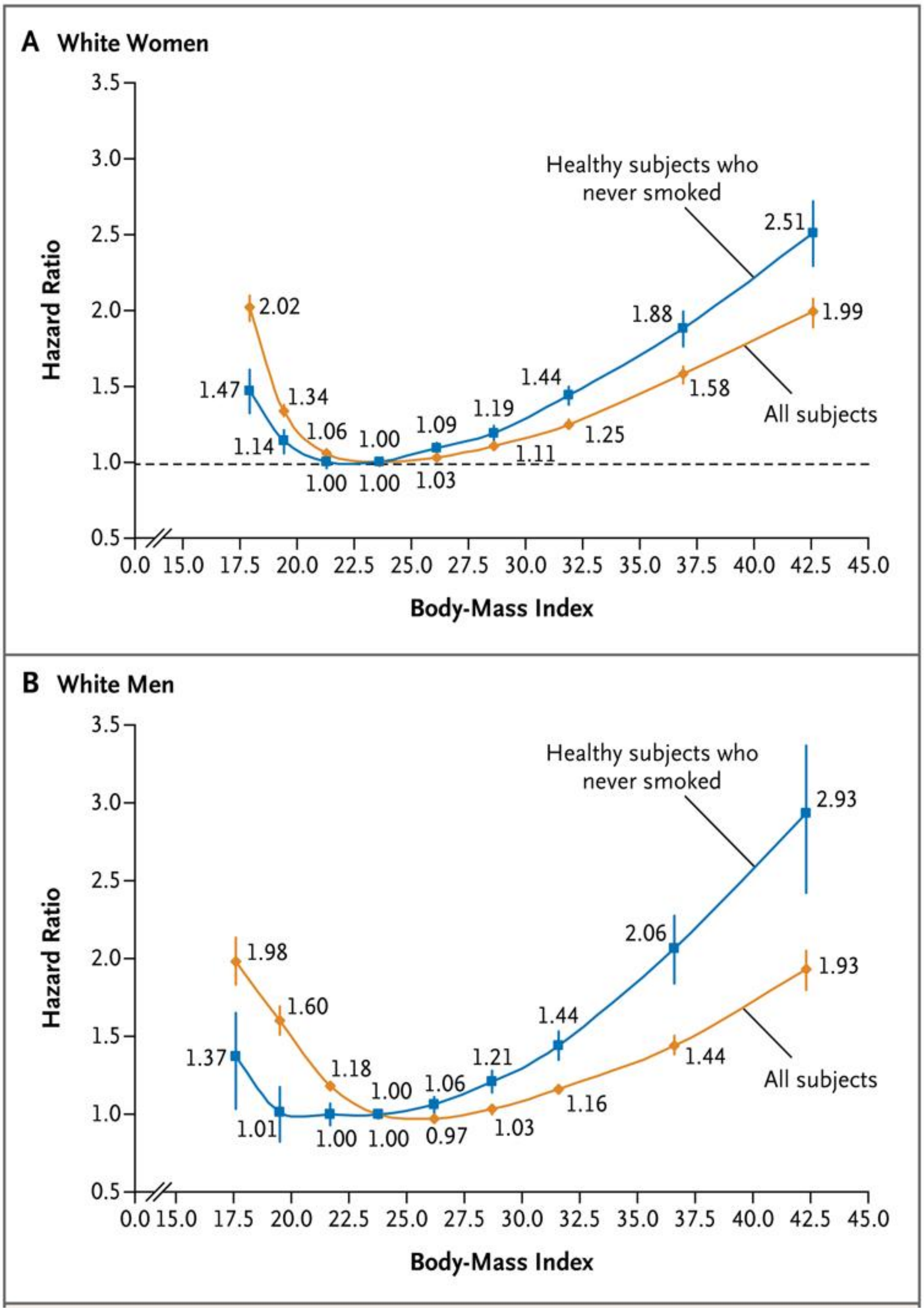


Fig 3.15 - Estimated hazard ratios for death from any cause according to BMI of healthy individuals. Reproduced from (Berrington de Gonzalez et al., 2010)

3.5 - Discussion

The aim of this study was to determine the association between BMI and mortality in a multiethnic population that had a first stroke.

In order to compare the prevalence of BMI categories between this study population and the healthy UK population, data from the National Diet and Nutrition Survey were used (table 3.16). The most recent report of this survey presents combined results from 3 years of the rolling programme (2008/09 – 2010/11) for a sample of the UK population designed to be nationally representative (NDNS, 2012).

Table 3.16 – Comparison of nutritional status (determined by BMI) between the SLSR population and the UK population

	SLSR population	UK population	
		Men	Women
underweight	6%	1%	2%
normal weight	39%	29%	39%
overweight, including	55%	70%	58%
obese	24%	26%	28%

Although excess weight has been recognised as a risk factor for stroke, the prevalence of overweight (including obese) individuals was slightly lower in the stroke population.
However, when compared with the prevalence of overweight and obesity (41.0% and 18.1%, respectively) in a Greek study with first-ever strokes (Vemmos et al., 2011), the prevalence of these BMI categories in the SLSR is greater.

It should be noted that all survival analyses conducted in different subgroups of this population demonstrated that BMI (both as a categorical and as a continuous variable) was a statistically significant independent risk factor for mortality after a first ever stroke.
Underweight patients had a significantly lower and overweight patients had a significantly higher survival, in both early (6 months) and late (up to 8 years) stages of follow-up period. When the analysis was conducted using 4 categories of BMI, the overweight group presented the lowest risk of mortality.

As mentioned in chapter 1, malnutrition has been shown to be a predictor of poor outcome in patients who have had a stroke and the association between underweight and a significantly higher risk of mortality was a consistent finding in all 8 studies of the review conducted in the introduction of this chapter (table 3.1), as well as in the present study. A very low BMI had an important prognostic implication for patients who had a stroke, independently of type of stroke, age, gender, ethnicity, severity of stroke and several risk factors.

In the current study, the difference in risk of mortality of the overweight group in comparison with the reference group was not significant after the adjustment for possible confounders, which may have possible explanations.

First, this may be due to the demographic characteristics of the study population. To our knowledge, this is the first study exploring the association between BMI and long-term mortality after stroke in a multiethnic population and, as discussed before, this association is ethnicity-dependent in healthy persons (Zheng et al., 2011). None of the 8 papers presented on table 3.1 (Olsen et al., 2008, Towfighi and Ovbiagele, 2009, Vemmos et al., 2011, Kim et al., 2011, Kim et al., 2012, Ryu et al., 2011, Dennis, 2003, Hassan et al., 2013) adjusted their results for the effect of ethnicity, probably because the studies were conducted in ethnically homogenous populations. Nonetheless, a study that examined survival differences in the SLSR underlined the importance of taking into consideration the effect of ethnic differences in survival after stroke (Wolfe et al., 2005); i.e., black patients were more likely to survive than white patients, even after controlling for several factors.

Second, the other possible reason for the lack of significant results is the relatively small sample size of this study. Studies that included thousands of patients were able to demonstrate significant differences in mortality risk (in each BMI group, when compared with the reference range), in ischaemic (Kim et al., 2012), haemorrhagic (Kim et al., 2011) or both types of stroke (Olsen et al., 2008, Vemmos et al., 2011).

Finally, the possibility of a selection bias cannot be excluded. Only 53% of the individuals included in the SLSR had a record of BMI, and when both groups with and without BMI were compared, it was observed that the second group had more deaths and more severe strokes. It is possible that patients did not have their BMI recorded due to practical reasons, i.e. in the case of a poor prognosis it might have been considered by the staff as unsafe or unethical to weigh the patient (although I will demonstrate in the next chapter that, with effort, it is possible to obtain information regarding weight current and height in all - or almost all - patients).

The same problem was also raised in other studies exploring the association between BMI and mortality in stroke patients. A study conducted in South Korea had to exclude 15.4% of their patients due to lack of BMI data (Kim et al., 2012) and, in the Danish cohort, BMI was measured in only 55% of the registered stroke patients and, from these, complete data was available for only 60% (Olsen et al., 2008). Nevertheless, this limitation is unlikely to affect results. In the Greek study, from the entire cohort of 2820 consecutive admissions to hospital with a first stroke (and registered in a stroke databank), only 1% were excluded because of lack of data regarding body weight or height or both, and their finding were similar, showing that overweight and obese individuals had significantly better survival rates than those with a normal BMI, at 1 week and at 10 years after stroke (Vemmos et al., 2011).

When analyses were conducted on groups of patients aged under and over 65, similar results were obtained in both groups: the risk of mortality was higher for the underweight individuals and there was a trend for a lower risk of death in those who were overweight, before and after the adjustment for possible confounders.

The lack of significant results in the overweight category (when comparing to the reference range) may be explained by the relatively small sample size of both groups.

While Towfighi and Ovbiagele suggested that the association between BMI and mortality is age-dependent in their analysis of 644 individuals with a self-reported stroke (Towfighi and Ovbiagele, 2009), the most recent study with 34132 acute ischaemic strokes conducted stratified analyses by age groups and results remained significant in all age strata (Kim et al., 2012). This South Korean study supported the idea that the obesity paradox after stroke is independent of age, as well as cause of death.

In the current study, using multivariable Cox regression model with all types of strokes, the effect of BMI on mortality was not affected by the removal of stroke risk factors (as confounders) from the model. This is in line with similar findings from a previous study (Olsen et al., 2008), which is not surprising as it could be argued that diabetes, hypertension and dyslipidemia are mediators between obesity and mortality and, therefore, should not be treated as confounders. However, the majority of the studies identified in the review have included risk factors as confounders in their models.

When analyses were conducted with BMI as a continuous variable, the risk of mortality was higher in the lowest range of BMI and decreased gradually until the overweight group. In the analysis without the 4 outliers, the lowest risk point was reached when BMI was 33.0 Kg/m^2, and after that, there was a modest elevation in risk of death for the BMI range of 35-50 Kg/m^2.

These findings suggest that weight management strategies targeting the optimal BMI range used for the healthy population may require further evaluation and individualization in secondary prevention of strokes. This also reinforces the need to identify and treat underweight patients (not only in hospital but also in the community) and the need to adopt strategies that avoid the development of malnutrition after stroke.

Limitations and strengths

Beside the limitation regarding the availability of BMI records, the method used to obtain the weight for those patients with a record of BMI included not only measured weight (49%) but also weight recalled by patient or a relative (34%) and weight obtained from medical records (17%).

It has been reported that underweight individuals tend to overestimate their weight and that overweight individuals tend to underestimate it but the validity of the reported weight is acceptable and there is small error (1-2%) in the classification of these individuals into BMI categories (calculated by measured versus reported weights) (Schmidt et al., 1993). Other studies have reported the need to use alternative sources of information to obtain patients' weight (Vemmos et al., 2011), and this is preferred over the option of excluding patients from the analysis, which could induce a selection bias.

The problem regarding quality of the data collection is also a limitation of the FOOD trial (Dennis, 2003), where only 20% of patients were weighed or had their BMI calculated and there was a lack of standardization of assessment of nutritional status, with a large proportion of patients having their nutritional status assessed informally (i.e. based on simple observation, as a bedside assessment).

The present study has a relatively small sample size but it has advantages over other studies that have explored the association between BMI and mortality after stroke.
The SLSR is a register designed to prospectively collect data on individuals who had a diagnosed stroke for the first time, constituting a good source of information for epidemiological studies. On the contrary, other studies are sub-analyses of an original study with specific inclusion and exclusion criteria, which may have biased the results (Kim et al., 2012, Kim et al., 2011), and another study selected their study participants based on self-reported history of stroke in a national survey of non-institutionalized individuals (Towfighi and Ovbiagele, 2009). Additionally, there was no information regarding the type of stroke and BMI was not assessed at the time that the individuals had the stroke.

Lack of analysis of specific subgroups (e.g. age or BMI categories) of the population is also a limitation of some studies.
The SLSR includes individuals of all ages. Contrary to the present study that includes young stroke patients aged over 18 years, Olsen et al decided to exclude patients under 40 years (Olsen et al., 2008).
Given the poor prognosis of underweight patients, it is important to analyse this group separately. Unfortunately, both studies conducted by Vemmos and Hassan (and their colleagues) merged the underweight with the normal weight group (and the overweight group in Hassan's study), which was used as a reference group (Vemmos et al., 2011, Hassan et al., 2013).
It should be noted that the majority of all these studies, including the present study, points out two important limitations, which are: BMI is the only measure of obesity (or indicator of nutritional status) and lack of assessment of weight or nutritional status change over time.

Future research could include the analysis of other data available on the SLSR, such as the follow-up information obtained at 1 year after stroke that may suggest changes in patients' weight since admission**.** This includes questions regarding the need for help with feeding, swallowing problems and any attempt at losing weight.

Contributions and lessons learnt from this study

In particular, this study enabled me to:

- learn to manage a large database from an ongoing population based stroke register, which records strokes occurring in a specific area of South London.
- learn to develop advanced statistical models, such as Cox Regression Hazards Models using BMI as a categorical and as a continuous variable, and the graphed relationship between BMI and long term mortality
- realise that BMI data were poorly collected and this may lead to a selection bias. For 47% of individuals, there were no complete records of weight, height or both parameters, and for the remaining 53% where BMI was available, different methods were used to obtain weight.
- realise that other variables that can be entered in the model as potential confounders (e.g. NIHSS score) were not available or were not collected for all patients and this excludes several patients (not necessarily randomly) between univariate and multivariable analyses
- understand that stratified analyses are limited in such a relatively small sample size. For example, in this sample of 856 patients, when I decided to conduct separate survival analyses in 2 groups of age (over and under 65 years, n= 547 and n=309 respectively), in the group of patients under 65 years, there were only 6 individuals who were in the underweight category. Therefore, results need to be interpreted with caution
- recognise that potentially important confounders (e.g. smoking) were not included in the multivariable analyses. I have not adjusted the results for the effect of smoking as this information was not available in the SLSR dataset that was provided to me.
- appreciate that BMI was the only indicator of nutritional status and mortality was the only outcome assessed in this study

Thus, I learnt that in a future, prospectively designed, study (chapter 4), I will need to:

- make an effort to collect BMI data for every recruited patient
- make an effort to collect data on potential confounders for every recruited patient. For example, if I see that the NIHSS was not applied to the patients that I recruited, I will need to request the consultants to retrospectively assess the severity of the stroke according to reported symptoms and neurological evaluation conducted on admission to hospital
- consider adjusting results for confounders such as ethnicity, age and type of stroke, instead of performing stratified analyses in subgroups of patients

- have a thorough selection of potentially important confounders not captured in this study (e.g. smoking) and collect these data for every recruited patient in the prospectively designed study
- include other indicators of nutritional status such as waist circumference and risk of malnutrition, as well as other outcomes such as LOS, hospitalisation costs and stroke recurrence

3.6 - Conclusions

This study showed that BMI is a significant risk factor for mortality in a multiethnic population of individuals who had a stroke for the first time. The association between BMI and mortality over a period of 8 years is represented by a J shaped curve, where the lowest risk is attributed to the overweight group.

However, further research is needed. In particular, it is important to evaluate other outcomes, such as the risk of having a recurrent stroke as well as other indicators of nutritional status and distribution of body fat, such as WC. A prospective study was therefore designed to investigate this (Chapter 4).

Chapter 4:
Nutritional status after stroke: a cohort study about the association between risk of malnutrition, BMI, central obesity and outcomes, 6 months after stroke

4.1 – Introduction

The purpose of this prospective observational study was to explore the relationship between nutritional status (both undernutrition and overnutrition) and post-stroke outcomes. The study was divided into 3 sub-studies, described below (A, B and C).

A. Risk of malnutrition and post-stroke outcomes

Malnutrition has been clearly identified as a problem that affects the outcomes of patients who have had a stroke and, as it was mentioned before (in “Chapter 1 - Introduction”), one way of identifying patients with nutritional problems that might be amenable to nutritional intervention is to use a validated NST.

To date, no published studies have validated a NST for use specifically in stroke patients (Foley et al., 2012, Cairella et al., 2004, SIGN, 2010) and this was identified as an area that lacks a strong evidence base in the most recent Scottish guidelines on the management of patients with stroke (SIGN, 2010).

Malnutrition Universal Screening Tool (MUST) is a NST, launched in 2003, which involves assessment of BMI, % weight loss and the effect of acute illness on dietary intake (Elia, 2003) and it has been suggested as an appropriate tool for patients who have had a stroke (RCP, 2012).

As mentioned in chapter 2, mortality and LOS data can be collected to establish the predictive validity of a NST, i.e., the ability of the tool to predict clinical outcomes. MUST has been suggested to predict clinical outcomes in elderly patients (Stratton et al., 2006) but the predictive validity of MUST in stroke patients is not yet known.

This study was designed to determine the ability of MUST to independently predict negative outcomes in acute stroke patients, more specifically mortality, LOS and readmissions at 6 months post stroke. If patients who are at risk of malnutrition are correctly and promptly identified, they should be more likely to benefit from nutritional support.

Moreover, malnutrition poses a significant burden on healthcare resources (Elia, 2006) and it has been suggested that disease-related malnutrition is an important determinant of hospitalisation costs (Amaral et al., 2007) but, to date, this association has not been tested in patients who have had a stroke. Thus, this study will also analyse the association between malnutrition and hospitalisation costs, at 6 months post stroke.

B. Comparison of two NST with regards to their performance to predict post-stroke outcomes

Different NSTs use different criteria to identify patients at risk of malnutrition and therefore may perform differently in the same patient group. For example, in a study conducted in a geriatric population, the proportion of patients with malnutrition varied between 6.5 and 85%, after using 7 different sets of diagnostic criteria (Joosten, 1999). Several different tools have been developed to screen for malnutrition and they include various important features. Hence, it is useful to compare their performance to predict relevant outcomes in a specific population.

The GSTT NST (described in chapter 2) is similar to MUST, however it includes a question on recent dietary intake that MUST does not and it does not require the quantification of weight loss. Given that both NST were being used in the hospitals where the data were collected, it was decided to apply both tools to each recruited patient. The aim of this study was to determine which NST best predicts mortality, LOS and hospitalisation costs at 6 months post stroke.

C. BMI, central obesity and post-stroke outcomes

As explained in chapter 1 ("1.1.3 – Obesity"), BMI may not be an accurate measure of adiposity in some adults, e.g. those who are highly muscular (and may be classified as "false obese"), which explains the need of having additional measures to identify obesity and its risks.

Thus, it is recommended that the assessment of health risks associated with overweight and obesity in adults should be based on BMI and WC (NICE, 2006b).

A few studies have explored the impact of body fat distribution on the risk of stroke.

In a study with 576 stroke patients and 1142 controls, Suk et al identified abdominal obesity - measured by waist-to-hip ratio - as an independent, potent risk factor (and stronger than BMI) for first ischaemic stroke, with a greater effect among younger people (Suk et al., 2003).

Another case-control study (379 cases with stroke and 758 controls) that used a number of markers of abdominal obesity, such as WC, waist-to-hip ratio and waist-to-height ratio, reported a similar strong and graded association of abdominal fat markers with the risk of ischaemic and haemorrhagic stroke or TIA (Winter et al., 2008). In this paper, authors concluded that WC and related ratios can better predict cerebrovascular events than BMI and the same findings are supported by a longitudinal study with more than 50000 healthy individuals who were followed-up for 11 years (Bodenant et al., 2011).

Other studies with large American (Jacobs et al., 2010) and European (Pischon et al., 2008) cohorts have examined the impact of body fat distribution on the risk of death in the general population and found that WC and waist-to-hip ratio were positively and strongly associated with all cause mortality.

The studies previously mentioned in chapter 2 that explored the impact of BMI on mortality after stroke (Olsen et al., 2008, Towfighi and Ovbiagele, 2009, Vemmos et al., 2011, Kim et al., 2012, Kim et al., 2011, Ryu et al., 2011, Dennis, 2003, Hassan et al., 2013) did not measure any indicator of body fat distribution and, to date, no published studies have reported an association between abdominal obesity and mortality (or other outcomes) post stroke.

The association between central obesity and mortality after stroke therefore remains unknown.

According to estimates of stroke incidence in England and Wales, every year 133,700 people have a stroke, of which 87,700 are first strokes and 53,700 are recurrent strokes (Carroll et al., 2001). This significant proportion of recurrent strokes (40%) justifies the importance of including recurrent events as an outcome in the current study.

Although recurrent strokes are not as easily recorded and traceable as mortality, a complete approach investigating the impact of BMI and abdominal obesity on clinical outcomes after a stroke should include stroke recurrence as one of the outcome measures.

A few studies have evaluated the impact of BMI on stroke recurrence but they have limitations, such as:

- the inclusion of only first strokes and combination of underweight and normal weight patients in one BMI group (the “lean” group) (Vemmos et al., 2011)
- the inclusion of TIAs (Doehner et al., 2013),

- being a sub-analysis of an intervention study with specific inclusion and exclusion criteria, which may have biased the results (Doehner et al., 2013, Ovbiagele et al., 2011),
- having a significant proportion of patients (36%) who were included in the study, but had no record of BMI (Andersen and Olsen, 2013).

4.2 – Aims and hypotheses

The following aims and hypotheses were established:

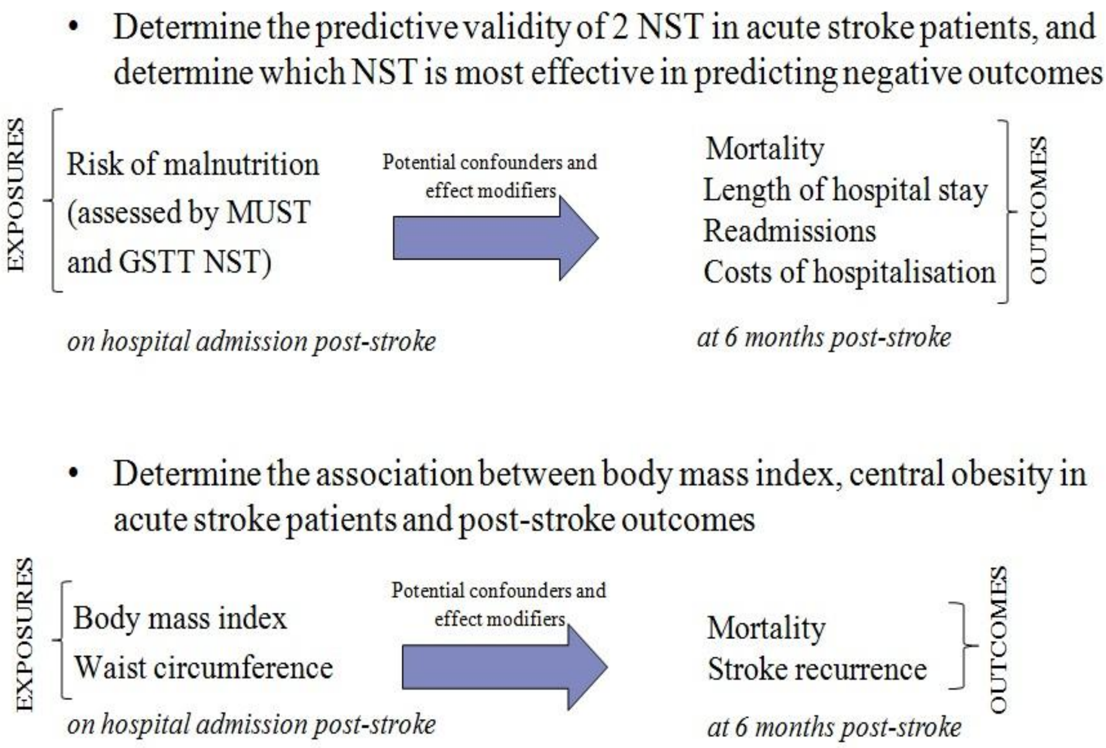
A. Aim: to determine the ability of MUST to independently predict negative outcomes in acute stroke patients, specifically mortality, LOS, readmissions and hospitalisation costs at 6 months post stroke.
The main hypothesis was that MUST can be used to predict risk of negative outcomes in stroke patients.
In particular, it was hypothesised that there is a significant difference in rates of mortality, LOS, number of readmissions and hospitalisation costs between patients in different malnutrition risk categories, at 6 months post stroke.

B. Aim: to determine whether MUST or GSTT NST is the most effective NST in predicting negative outcomes in patients at 6 months post stroke.
The main hypothesis was that MUST and GSTT NST have different performance in predicting negative outcomes and, therefore, have a different predictive validity for mortality, LOS, readmissions and hospitalisation costs, at 6 months post stroke.

C. Aim: to determine the association between BMI, central obesity and outcomes (i.e. mortality and recurrent stroke) at 6 months post-stroke.
The main hypothesis was that there is a significant difference in the risk of mortality and risk of stroke recurrence between patients in different BMI and WC categories, at 6 months post-stroke.

The following figure summarises the aims of the study and the variables included for each aim.

Fig. 4.1 a) - Aims of the study and the variables included for each aim



4.3 - Methods

4.3.1 – Recruitment, inclusion criteria, ethical considerations and baseline data collection

This was an observational prospective (cohort) study, which was hypotheses-generating. It generated data to facilitate the design of adequately-powered randomised, controlled clinical trials, e.g. to study whether nutritional support given to patients identified as being at risk of malnutrition improves patients' clinical outcomes.

Recruitment

Recruitment started on 13th June 2011 at St. Thomas' Hospital (located in Lambeth) and on 22nd November 2011 at Princess Royal University Hospital (located in Bromley), and finished on 18th May 2012. During this period, all patients consecutively admitted to the hyper-acute stroke units (HASU) or SU of both hospitals were screened for eligibility for this study.

HASUs provide the immediate response to a stroke, where the patient is stabilised and receives primary intervention. The patient´s LOS is typically no longer than 72h, and after this time (or when they are medically stable), they are moved to SUs closer to their place of residence that will provide a multi-therapy rehabilitation (NHS, 2008).

Inclusion criteria

The principal inclusion criterion was having a diagnosis of stroke (ischaemic or haemorrhagic), confirmed by a CT scan, a magnetic resonance imaging scan or the consultant's clinical judgment, as well as having an NHS number (a requirement to track the patient 6 months subsequent to recruitment).

All patients admitted to the SU and HASU of STH and Princess Royal University Hospital following an acute stroke were considered eligible for inclusion, and they were considered ineligible if they fulfilled any of the following criteria:

- Non-adults (less than 18 years old) or pregnant women
- Diagnosis of TIA (as explained before, a TIA gives a clinical picture similar to a stroke except that it is transient (less than 24h) and reversible)
- "Stroke mimics", which is the term employed for manifestations of nonvascular disease processes when a stroke like clinical picture is produced
- Patients without an NHS number, which is usually recorded on the hospital computerised records

Ethical considerations

Ethical approval was obtained from the "National Research Ethics Service for Yorkshire and the Humber – Leeds West", in May 2011 (reference number 11/YH/0054) - appendix 4.1. This committee covers research involving adults who may lack capacity. Local approvals from both R&D departments at GSTT and at South London Healthcare NHS Trust were obtained during the following month.

Once the diagnosis of stroke was confirmed, a member of the clinical care team evaluated whether the patient was able (not incapacitated) to give permission to speak with the researcher and able to consent to participate in the study.

After obtaining permission, the study was briefly introduced to the patient by the researcher (regarding aims, objectives and conduct of the study) followed by the delivery of the patient information booklet (appendix 4.2). Patients and carers were given the opportunity to ask questions and were allowed up to 24 hours to decide whether or not they wish to take part in the study.

If the patient was incapacitated or confused, a discussion with his/her consultant took place to identify the most appropriate consultee from whom to seek advice (e.g. next of kin or close relative).

Once the patient (or his/her consultee, for patients who were incapacitated or confused) decided they wished to take part in the study, written consent/advice was obtained on a standard pro forma (appendices 4.3 and 4.4). All signed consent forms were kept in a lockable cabinet in the Departments of Nutrition & Dietetics at St Thomas' Hospital, 1 copy was filed in the patient's medical notes and another copy was given to the patient or his/her consultee.

All patients who consented to be part of the study were also handed a "next of kin information letter" (Appendix 4.5) confirming their agreement to be in the study and summarizing the research process. The study participant was advised to hand this letter to a close relative or friend. This procedure complies with the requirements of the Mental Capacity Act with regards to patients who lose capacity during the study period.

Baseline data collection

All subjects admitted at the SU and HASU of both hospitals were recorded on a "Recruitment Log" sheet. Those who fulfilled the inclusion criteria and gave consent/assent were allocated a unique identifier (study ID number), which was recorded on all data collection sheets. Details that could make the subject identifiable e.g. name, date of birth, hospital number and NHS number were recorded in a "Master list" that was kept in a lockable cabinet in the Dietetic Department at STH.

Recruitment and baseline data collection were aimed to be completed within 3 days of admission, at both hospitals (to maximize recruitment and allow for a greater heterogeneity of patients). Data collection sheets (appendix 4.6) were used to collect information:

- from the medical notes:

- date of admission,
- date of stroke
- gender
- ethnic group
- type of stroke
- living conditions prior to stroke (support includes formal support e.g. from social services, and informal support e.g. from family or friend).
- medical history as identified by the medical team, potentially relevant as stroke risk factors and chronic conditions likely to affect nutritional status prior to admission.

For "cognitive dysfunction" and "impaired mobility", these conditions were only recorded if they were present prior to current admission, as they may be affected by stroke. For all other conditions, they were recorded if the disease was present prior to current admission or if it was newly diagnosed during hospitalisation.

The first 9 items are well known risk factors for stroke and the last 3 items are chronic conditions that are likely to affect nutritional status prior to admission. Gastrointestinal diseases include Crohn's disease, pancreatic insufficiency, irritable bowel syndrome, etc.

- record of previous stroke
- NIHSS score, i.e., the result of a routinely applied scale that measures the severity of stroke (appendix 4.7)
- Swallow test result, i.e., the result of the routinely applied swallow test, aimed to detect swallowing problems in patients with a suspected stroke, on admission to hospital (appendix 4.8).

- from the nutritional screening tools that are routinely used in both hospitals (appendix 2.1 and 4.9, and table 4.1 a)):

- Patient's height. This was measured using a portable stadiometer (Seca, Leicester, UK), according to standard methodology, in patients who could mobilise safely and were able to stand. In patients who were unable to stand, recalled height (if judged to be reliable and realistic) or a surrogate measure, i.e. height estimated using ulna length, was used to calculate height. Ulna length was measured between the olecranon process and the styloid process, as described by the MUST explanatory booklet (Elia et al., 2003).

- Patient's current weight. This was measured using Seca clinical scales, either chair or hoist scales, regularly calibrated, with patients wearing light clothing and without shoes. When weight could not be measured (e.g. in case of a recent hip fracture), recalled weight (if reliable and realistic) was used. The presence of oedema and any record of a previous amputation were documented and weight was corrected accordingly.

- Patient's usual weight. This was obtained from the patient, the relative or carer and medical notes, some of which had weight records from previous hospital admissions, outpatient appointments and visits to General Practitioners.

- Unintentional weight loss in the last 6 months (affirmative or negative) for the GSTT NST, or unintentional weight loss in the past 3 to 6 months (<5%, 5-10% or > 10%) for the MUST. Usual (previous) and current weights were used to calculate percentage of weight change according to the following equation:

$$\%\text{ weight change} = \frac{\text{usual weight (Kg)} - \text{current weight (Kg)}}{\text{usual weight (Kg)}} \times 100$$

- Loss of appetite/decrease in dietary intake in the last 6 months (for the GSTT NST), as reported by patient, relative or carer, and medical notes.

- Inability to eat or "nil by mouth" for more than 5 days, as described in medical notes.

- As a new parameter (not collected routinely): WC.

The measurement was standardised at the midpoint between the lowest rib and the iliac crest and, when possible, was taken on patients with their waist uncovered. Participants were asked to breathe normally and the reading was taken at the end of a normal exhalation.

In subjects who were safe to stand WC was measured while they were standing and, for those with a good mobility, the same measurement was also taken in the supine position (with patients lying down on the bed), in as many patients as possible. For patients who were confined to bed, WC was only measured in the supine position (if possible, without causing physical or psychological distress).

A direct comparison will be made between the WC measurements obtained from patients standing and in the supine position, enabling inferences to be made about the validity of measurements obtained from patients who are bed-bound.

Table 4.1 a) - Factors included in assessment of nutritional risk according to MUST and GSTT NST

	MUST	**GSTT NST**
Unintentional weight loss in the last 6 months	Yes, quantified into: < 5%, 5-10%, >10%.	Yes, not quantified: "yes" or "no"
Unintentional reduced intake/appetite in the last 6 months	No	Yes
Body Mass Index (Kg/m^2)	Yes, with 3 levels of score: < 18.5, 18.5-20, >20.	Yes, with 2 levels of score < 18.5, ≥18.5
Nil by mouth or inability to eat for more than 5 days	Yes, in the presence of acute disease	Yes
Patient on tube feeding or parenteral nutrition **Grade 3-4 pressure sores**	No No	Yes. These parameters are considered to be at high risk of malnutrition (equivalent to score ≥ 4) because of local policies, i.e., at GSTT patients on tube feeding or parenteral nutrition or with grade 3-4 pressure sores should be automatically referred to a dietitian

All the equipment was cleaned and disinfected after use, and disposable tape measures were used for patients who were isolated (as in some cases, isolation was needed to prevent the transmission of infectious diseases).

With regards to the baseline data collection, and in particular the data from the NSTs, it must be noted that both tools were applied by the same person (the author), allowing for a standardized methodology of data collection.

This also prevents missing data that is frequently observed in clinical settings. For example, patients must be weighed on admission to hospital and, unless they are severely

ill, this is done and recorded on the NST and on the “weight chart”. However, in the vast majority of the cases, the NST was not fully completed by the staff (e.g. "usual weight" and "actual height" fields were frequently left uncompleted).
Old case notes were available for the majority of the patients and were thoroughly reviewed to obtain potentially useful information. In several cases, patients’ General Practitioners were contacted (by fax) to obtain information on previous medical history and medication, which would also contain additional information on previous weights and heights measured during routine appointments. All these data were used to inform about previous and validate current measurements concerning nutritional status. In summary, a variety of information sources was utilized to gather the baseline data, which was consistently collected by the author.

The number of patients who could not be weighed or measured due to severity of their clinical condition was recorded, and when there was no alternative method to obtain these data. When alternative methods were used, their validity was analysed and discussed. All efforts were made to recruit all eligible patients and to collect all the baseline data for every recruited patient. The follow-up procedure (described in the following section) was chosen to minimise loss of data from recruited patients. All these factors are crucial to minimise potential sources of bias.

4.3.2 – Follow-up procedure

This study was designed to have a minimal impact on patients, and to recruit as many individuals as possible. Thus, after recruitment and collection of the baseline data, patients were not contacted again. The data regarding outcomes of each patient for a follow-up period of 6 months after the stroke were obtained from the Summary Care Records and the Hospital Episode Statistics (HES) databases. The NHS number was used to track each patient in both systems.

The primary outcome - 6 month mortality - was obtained through the Summary Care Records, an electronic patient record that stores a defined set of key patient data for every patient in England. These data make a summary record created from information held on GP clinical systems, from basic demographic data to date of death (when applicable).

Mortality data is quickly updated, through notifications from GPs, hospitals and register of deaths.

Access to data is available to NHS personnel anywhere in England, but only if they have the correct access rights on their smartcard approved by senior management. After receiving the training and authorization to use a smartcard, mortality data were collected for each patient on 18th December, 2012 (one month after the 6-month follow-up period of the last recruited patient, as recommended by the Summary Care Records system to guarantee that all death notifications were received and recorded).

HES is a data warehouse containing details of all admissions, outpatient appointments and A&E attendances at NHS hospitals in England. Through a tailor-made report requested from HES, and after gaining the adequate approval in March 2013, a database was received in April 2013. HES is not a live system; there is a time lag of around 6 months (which justifies the reception of the data in April 2013) between the hospitals submitting the data to HES and the time point when the data can be accessed. This is because various data quality checks and validations are applied to the data, which is then cleansed prior to release.

We requested information from the inpatient data set, which is the most commonly used and holds data from 1998 onwards. It is patient based, and is made up of records for each period of care under one consultant (episodes). Each episode is made up of information relating to the patient such as age, sex, ethnicity and home postcode; the treatment journey such as admission and discharge dates, diagnoses, operations, and information relating professionals associated with the patient’s care. Data (fields) requested to HES can be found in appendix 4.10.

Once the database was received, the information was organized by patient, in such a way that could allow for the calculation of each patient’s cumulative LOS, number of re-admissions, recurrent strokes and hospitalisation costs. It was also cleaned and validated against the information collected on baseline/recruitment. Any issue or disagreement was discussed directly with the HES data linkage team, via e-mail or telephone.

This follow-up method helps to identify any NHS hospital related event that may occur anywhere in England. For example, a patient who lives in Manchester and has a first stroke in London while visiting this city, is recruited at the London-based hospital where he/she was admitted. After returning to Manchester, if the patient has another hospital admission and/or a stroke in a period of 6 months, this follow-up procedure (i.e. using HES data) will identify these potential events. In contrast, hospital computerised medical records are not able to capture admissions that occur in another hospital.

Analyses on cumulative LOS, hospitalisation costs, hospital readmissions and stroke recurrence were conducted on patients who survived at 6 months post stroke. Patient centred outcomes such as functional disability and quality of life were also considered, but it was decided not to include them for the reasons explained in section “4.5 – Discussion”, under “Limitations”.

The cumulative LOS is the total number of days spent in hospital during the follow-up period. In other words, it is the sum of days in each hospital admission (including the initial admission after recruitment), during 6 months post stroke, for those patients who survived.

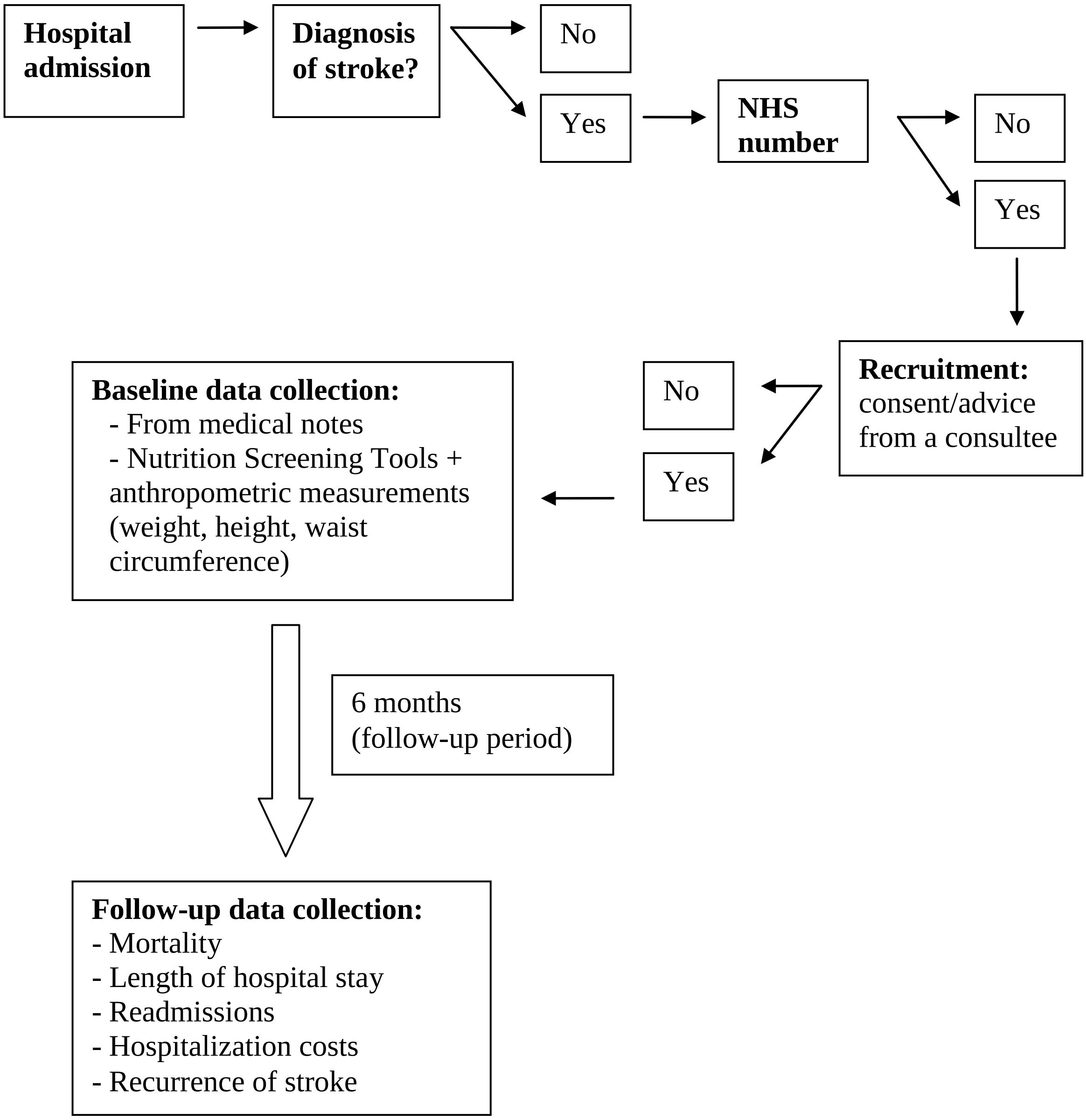
Analyses of hospitalisation costs comprised the cost estimation of all hospital admissions that each surviving individual had over a period of 6 months post stroke.

Diagnoses codes for inpatients are grouped into Healthcare Resource Groups (HRG), which are standard groupings of clinically similar treatments that use common levels of healthcare resource. HRGs were supplied by HES for every hospital admission of patients included in the present study.

The cost analyses were based on the “Payment by Results” system. This is the hospital payment system in England in which commissioners pay providers (NHS trusts, etc.) a national tariff for admitted patient care, outpatients and A&E.

The “2012-13 tariff information spreadsheet” (Department of Health, 2012) was used to transform the HRG (from the database provided by HES) into the tariffs paid by the commissioners, for each patient. These cost analyses included relevant adjustments to the tariffs for length of admission (long or short stays) and for type of admission (elective or non-elective), but excluded the adjustment for the market forces factor and the specialised services increment, as this is not applicable for the purposes of this study aim, i.e. we aimed to know whether being nutritionally vulnerable increases hospitalisation costs, independently of the Trust and geographical area where patients are admitted to.

The following figure (fig. 4.1) shows the design of the present study.



NHS = National Health Service

Fig. 4.1 - Study design

4.3.3 – Statistical analysis and sample size calculation

1. Patients were classified into:

- 3 nutrition risk categories, according to MUST and GSTT NST scores: low, medium and high.
- 4 BMI categories: less than 18.5 kg/m^2 (underweight), 18.5 to 24.9 kg/m^2 (normal weight), 25.0 to 29.9 kg/m^2 (overweight) and 30.0 kg/m^2 or more (obese).
- Quartiles of WC

2. Baseline characteristics of NST, BMI and WC categories were compared using the Chi-square test for categorical variables and the ANOVA or the *t*-test for continuous variables. Outcome data were tested for normality using the Kolmogorov-Smirnov test and, when needed, were log-transformed.

3. The Chi-square test was conducted to compare categorical outcomes (e.g. mortality rates) between BMI, WC and nutrition risk category.

In order to compare continuous variables (e.g. LOS) between categories, non parametric tests (e.g. Kruskal-Wallis or Mann-Whitney tests) were used for the non-normally distributed data and parametric testes (e.g. ANOVA) were used if data fitted the normal distribution.

A post-hoc analysis to assess the effect of possible confounders (e.g. ethnicity, age, gender, type and severity of stroke, stroke risk factors) on outcomes included a binary logistic regression and univariate analysis of variance.

4. Cox Proportional Hazards Models were used to compare risk of mortality (crude and adjusted HR, with 95% confidence intervals (CIs)) between categories of BMI, WC and risk of malnutrition. Multivariable models allowed for the adjustment of several covariates, such as age at time of stroke, gender, ethnicity, type and severity of stroke, and stroke risk factors.

The "normal weight" group, the first quartile of WC group and the "low risk of malnutrition" group were used as the "reference category", for models containing BMI, WC and risk of malnutrition, respectively.

Further analyses were conducted with subgroups of stroke subtype and age, and also with BMI as a continuous variable.

5. Both NST were compared for their ability to predict negative outcomes by using the area under the receiver operating characteristic (ROC) curves.

6. Sensitivity analyses were conducted as needed, e.g. to handle missing data: 2% of the HRG codes provided by HES were not valid or there are no published tariffs for these codes and, therefore, admissions or episodes linked to these codes were excluded. The 35 patients who had one admission with an invalid code or a code with no published tariff were identified, to allow for a sensitivity analysis (i.e. to conduct the cost analyses with and without those 35 patients). Also, the definition of recurrent stroke was analysed in different ways (i.e., including and excluding patients who died at 6 months) and the same applies to the definition of BMI (i.e., analyses were conducted using BMI as a categorical and as a continuous variable).

Statistical analyses were carried out using SPSS software version 19.0 for Windows (Chicago, Illinois, USA). Any differences were considered significant when $p < 0.05$.

Sample size calculation

Assuming 20% patients are malnourished on admission to the Stroke Unit (Davalos et al., 1996), and that 21% of patients die during the first 6 months after a stroke, being 35% deaths on malnourished patients and 20% in the adequately nourished (data from the FOOD Trial Collaboration, (Dennis, 2003)), a total sample size of 539 subjects was required to achieve a power of 95%, to detect a difference in mortality between malnourished and adequately nourished patients, with a significance level of 0.05 in a two-tailed Chi-squared test.

The G-Power Software (Erdfelder et al., 1996) was used to perform this calculation.

4.4 - Results

From screening to recruitment

During the 11-month recruitment period, 925 patients were admitted and screened at both hospitals: 361 at St. Thomas' Hospital and 564 at the Princess Royal University Hospital.

550 patients were recruited for this study and the remaining were not recruited for the following reasons:

1) Did not have a stroke: n = 289

Patients were admitted to the HASU but they did not have a stroke and received other diagnoses, such as: TIA, epileptic attack, seizure activity, migraine, alcohol intoxication, Bell's palsy, multifocal motor neuropathy, systemic lupus erythematosus; old stroke, subdural haemorrhage, small vessels ischaemic changes.

2) It was not possible to follow-up because:

- patients had a stroke but did not have a NHS number. It should be noted that London has several "visitors" and recent immigrants who are not registered with a GP; this was more common at St. Thomas' Hospital (n = 16) than at Princess Royal University Hospital (n=4), due to the central location of the first: n = 20

- had a stroke and a NHS number but moved to his home country after discharge, which makes it impossible to obtain the follow-up data: n = 1

3) Had a stroke and a NHS number and recruitment was discussed, but patients or their relatives/carers did not provide (i.e., refused to) consent: n = 5

4) Had a stroke and a NHS number but were discharged before being seen or approached for the present study, due to a quick transfer to a step-down rehabilitation unit (usually close to their residence), immediately after receiving the diagnosis (less than 2 days): n = 11

5) Had a stroke and a NHS number, and there was an attempt to approach these patients with regards to the study but they were unable to consent (e.g. due to presence of aphasia or not being alert) and there were no visits from relatives, friends or carers who could provide consent on their behalf: n = 16

6) Had a stroke and a NHS number, but patients were not weighed within the first 3 days after stroke due to the severity of illness. The majority of them were put on the Liverpool Care Pathway, which is a care pathway that a patient can expect in the final days and hours

of life. In other words, they were not for active treatment, and weighing the patient was not considered an option: n = 21

7) Had a stroke and a NHS number but were recruited before, i.e., these were recurrent strokes of patients previously recruited to this study: n = 12

In total, 925 screened patients – 289 – 20 – 1 – 5 – 11 – 16 – 21 – 12 = 550 recruited patients.

The percentage of eligible stroke patients (which also excludes those on LCP) who could not be recruited was only 5%.

Furthermore, 7 out of the 550 patients were recruited and, later, withdrawn from the study. For 6 patients their final diagnosis (after being submitted to further exams and assessments) was not a stroke; for the other patient, his family decided to take him back to his home country, making it impossible to obtain information about his outcomes.

Thus, the number of patients included in this study is 543 (n = 550 – 7 = 543).

The following figure summarizes the consort-type diagram of the study, from screening to recruitment (fig. 4.2).

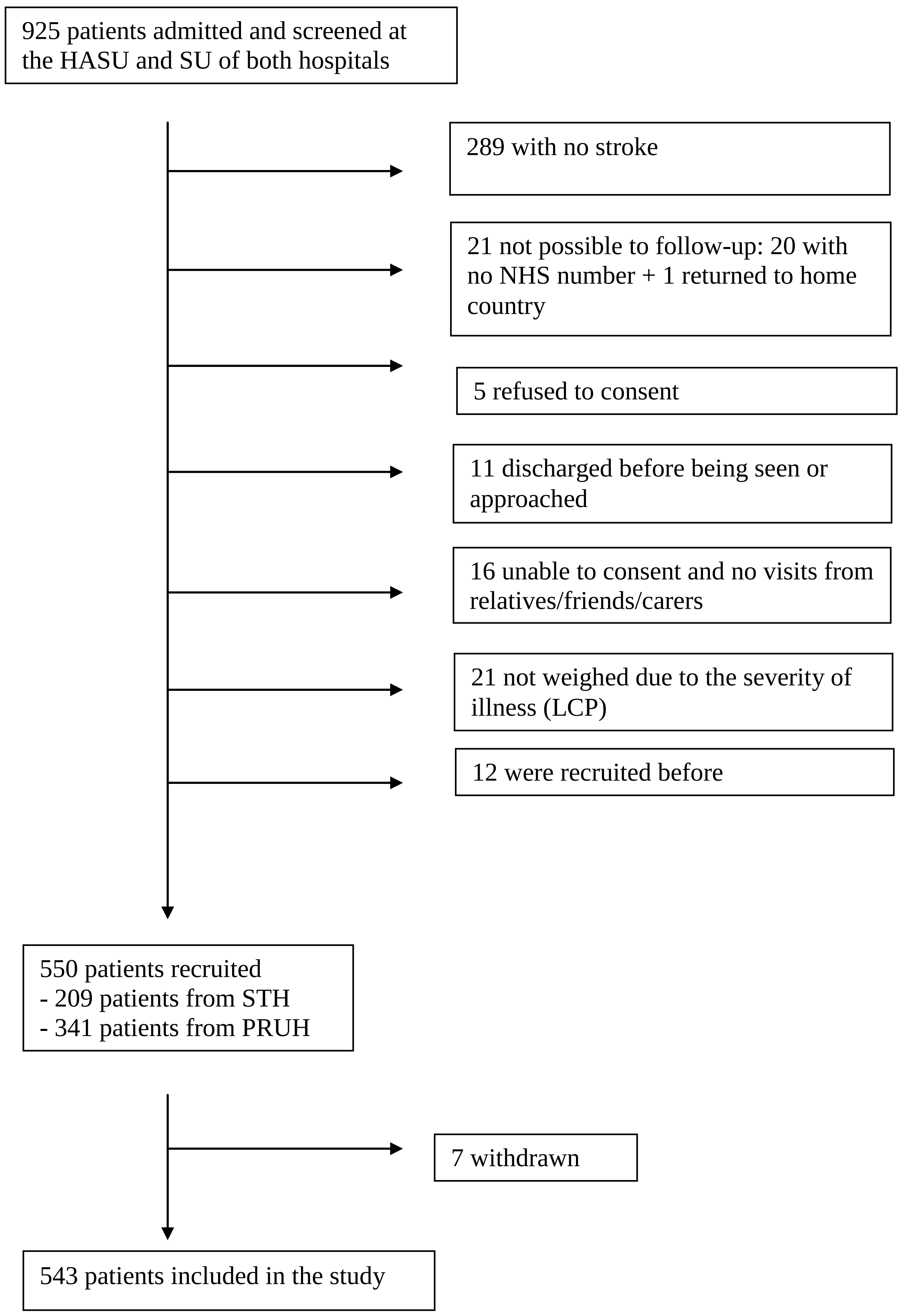


Fig. 4.2 – Consort-type diagram of the study

Baseline characteristics

a) Missing data

There were no missing data from variables collected at baseline and follow-up, except for:

- WC in 1 patient who refused to be measured, and
- MUST score in 6 patients where it was impossible to quantify weight loss, because this information could not be obtained from any source.

Therefore, the analysis for BMI and GSTT NST score related to 543 patients, while analysis related with WC related to 542 patients, and analysis related with MUST score contained 537 patients.

b) Characterisation of the study population

The 543 patients included in the study had a mean age of 74.7 years, 51 % were men, 87% had an ischaemic stroke, 80% were white, 22% had a previous stroke and 34% failed the swallow screening test on admission to hospital.

Characteristics of the study population (n=543) are detailed on table 4.1.

Table 4.1 – Baseline characteristics of patients included in the study (n=543)

Age, mean in years (SD)	74.7 (13.9)
Range (minimum-maximum)	22 - 99
Gender, n	
Male, n (%)	278 (51)
Female, n (%)	265 (49)
Ethnicity, n	
White, n (%)	437 (80)
Black, n (%)	79 (15)
East Asian, n (%)	10 (2)
South Asian, n (%)	14 (3)
Mixed ethnic background, n (%)	3 (1)
Any other background, n (%)	0
Type of stroke, n	
Ischaemic, n (%)	472 (87)
Haemorrhagic, n (%)	68 (12)
Subarachnoid haemorrhage, n (%)	3 (1)
Unclassified, n (%)	
NIHSS score, mean (SD)	7.6 (5.7)
Range (minimum-maximum)	(0-27)
Living conditions prior to stroke	
Home (unsupported), n (%)	124 (23)
Home (with support), n (%)	382 (70)
Institutionalized, n (%)	7 (1)
Other, n (%)	30 (6)
Medical History	
Hypertension, n (%)	375 (69)
Diabetes, n (%)	116 (21)
Dyslipidemia, n (%)	161 (30)
Smoking, n (%)	65 (12)
Ischaemic heart disease, n (%)	75 (14)
Heart failure, n (%)	16 (3)
Atrial fibrillation, n (%)	128 (24)
Previous TIA, n (%)	61 (11)
Heavy alcohol consumption, n (%)	24 (4)
GI diseases, n (%)	52 (10)
Cognitive dysfunction, n (%)	37 (7)
Impaired mobility, n (%)	62 (11)
Had a previous stroke	119 (22)
Failed swallow screening test	185 (34)

Numbers in parentheses indicate percentages for categorical data and SD (standard deviation) for continuous data; NIHSS = National Institutes of Health Stroke Scale

c) Anthropometric data

Weight was measured on admission to hospital in 542 patients. It was not possible to weigh one patient who was bed-bound following a recent fracture in the neck of femur. However, the patient had been weighed 2 weeks before admission to a hospital setting (before a surgery) and this was used as the current weight.

Height was preferentially measured, as described in section 4.1 “Methods - Baseline data collection”. Due to safety issues and limited mobility in the acute stage post-stroke, recalled height had to be used for several patients (n=342), and this was compared against recent documented height (when available). It has been suggested that self-reported height is valid for identifying relationships in epidemiological studies (Spencer et al., 2002).
39 patients were not able to stand safely to have their height measured and were not able to recall their height; therefore, ulna length was measured to estimate their height, as recommend by the MUST explanatory booklet (Elia et al., 2003).

WC was preferentially measured with patients standing (n=338), as described in section 4.1 “Methods - Baseline data collection”. For patients who were confined to bed (n=204), WC was only measured in the supine position. In a proportion of patients (n=77), WC was measured while they were standing and also in the supine position, and both methods were compared to make inferences about the validity of measurements obtained from patients who were bed-bound.

A Pearson product-moment correlation coefficient was computed and showed that there is a strong positive correlation between both methods of measuring WC (r=0.997, p<0.001). A paired t-test revealed a very small consistent bias (mean difference 0.29 cm, p=0.03), which is of little practical significance.
The differences between both methods are represented on the Bland-Altman plot (fig. 4.3) showing that in 95% of the cases the difference was not more than 2cm, and the variation was slightly higher at the upper end of the plot, i.e., in patients with larger WC (greater than 100cm), as expected.
Thus, WC of patients in the supine position was considered to be an acceptable and valid measurement, in cases where they were unable or unsafe to stand.

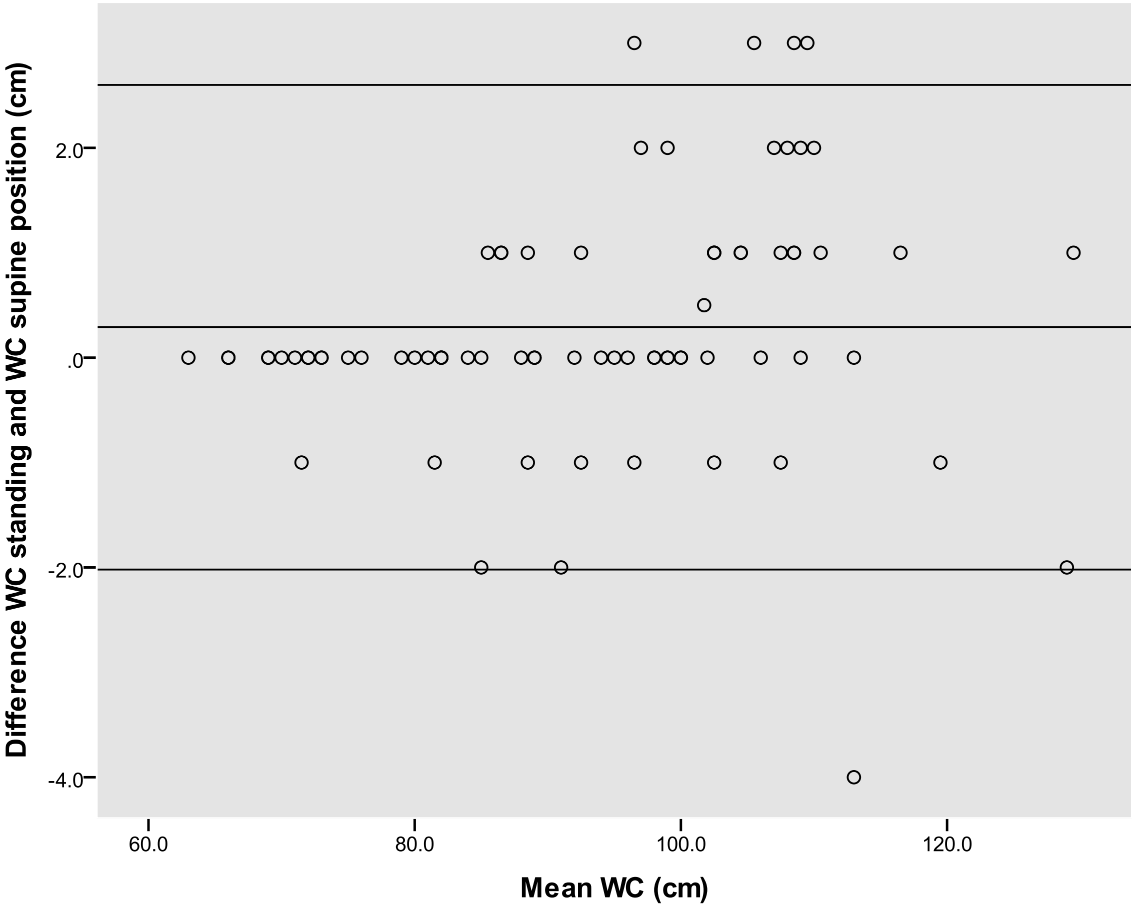


Fig. 4.3 - Bland-Altman plot representing the differences (in cm) in waist circumference measurements and average values of patients standing and in the supine position. The middle horizontal line represents the mean of the differences between both measurements and the other 2 horizontal lines correspond to the limits of agreement (mean ± 1.96 x standard deviation).

d) BMI, WC and risk of malnutrition

Table 4.2 shows the distribution of patients into groups of BMI, WC and risk of malnutrition. 55% of patients were overweight or obese (n=299), and approximately 30% of patients were at high risk of malnutrition, according to MUST (n=156) and GSTT NST (n=171). It is noteworthy that patients at high risk of malnutrition also included overweight and obese individuals: 29 (19%) overweight and 21 (14%) obese patients using MUST; 39 (18%) overweight and 19 (11%) obese patients using GSTT NST.

Table 4.2 – Distribution of patients into groups of BMI, WC and risk of malnutrition (as assessed by MUST and GSTT NST)

	Groups	Criteria	n	%
Body mass index (kg/m2)	underweight	<18.4	38	7.0
	normal weight	18.5 to 24.9	206	37.9
	overweight	25.0 to 29.9	177	32.6
	obese	>30.0	122	22.5
Waist circumference, gender specific (men / women, in cm)	1st quartile	<91.5 / <84	143	26.4
	2nd quartile	91.6-100 / 85-94	139	25.6
	3rd quartile	101-109 / 95-107	132	24.4
	4th quartile	>110 / >108	128	23.6
Malnutrition Universal Screening Tool	Low risk	Score = 0	342	63.7
	Medium risk	Score = 1	39	7.3
	High risk	Score ≥ 2	156	29.1
Guy´s and St Thomas´ NHS Foundation Trust Nutrition Screening Tool	Low risk	Score = 0	320	58.9
	Medium risk	Score = 2	52	9.6
	High risk	Score ≥ 4	171	31.5

Outcomes

Results are presented by outcome, which were determined for each patient at 6 months after the stroke.

a) Mortality

The Chi-square test was used to compare rates of mortality and Cox Proportional Hazards Models were used to compare risk of mortality (crude and adjusted HR) between categories of BMI, WC and risk of malnutrition. Baseline characteristics (such as age, gender, ethnicity, type and severity of stroke) and stroke risk factors were included as covariates in the multivariable model, as they may have an influence on outcome (mortality).

Results are summarized in the following tables and figures.

Table 4.3 - Rates of mortality and risk of mortality according to groups of BMI and quartiles of WC, using univariate and multivariable Cox Proportional Hazards Models

Mortality rates and hazard ratios	**n**	**Mortality rates**	**Univariate Cox Proportional Hazards Model**		**Multivariable [a] Cox Proportional Hazards Model**	
		(Chi-square test)	**Hazard ratio**	**95% CI**	**Hazard ratio**	**95% CI**
Body Mass Index categories	543	*p=0.001*	*p=0.001*		*p=0.057*	
Underweight	38	28.9%	1.18	0.62-2.28	0.82	0.41-1.65
Normal weight	206	23.8%	Reference group		Reference group	
Overweight	177	12.4%	0.48	0.29-0.79	0.57	0.33-0.97
Obesity	122	10.7%	0.40	0.22-0.74	0.46	0.24-0.88
Waist Circumference Quartiles	542	*p=0.046*	*p=0.044*		*p=0.107*	
1st quartile	143	25.2%	Reference group		Reference group	
2nd quartile	139	15.8%	0.60	0.35-1.02	0.64	0.37-1.09
3rd quartile	132	14.4%	0.54	0.31-0.94	0.59	0.33-1.06
4th quartile	128	14.1%	0.51	0.29-0.91	0.52	0.29-0.94

a - *results were adjusted for the effect of age, gender, ethnicity, type of stroke, severity of stroke and stroke risk factors (hypertension, diabetes, dyslipidemia, smoking, IHD, heart failure, atrial fibrillation, previous TIA and heavy alcohol consumption)*

There was a significant difference in mortality rates between patients in the 4 groups of BMI and WC (*p<0.001* and *p=0.046*, respectively). In the current study, the higher the BMI and the WC quartile, the lower the mortality rates.

Similarly, risk of mortality was significantly different between categories of BMI and WC (*p<0.001* and *p=0.044*, respectively). The underweight group and the 1st quartile of WC presented the highest risk of mortality; the obese group and the 4th WC quartile presented the lowest risk. The survival curves for both parameters are displayed on figure 4.4 and 4.5.

After taking into consideration all the potential confounders in the multivariable analyses, there was a trend for a statistically significant association between BMI and mortality (*p=0.057*), but the association between WC and mortality was no longer significant (*p=0.107*). Details regarding the effect of different variables on 6-month mortality can be found in appendix 4.11 a) and b).

The small number of underweight patients explains the wide confidence intervals of the underweight group, and the non-significant decreased risk has to be interpreted with caution. It can be concluded that, having the normal weight category as a reference group, being overweight was associated with a 43% decreased risk of death and with a 54% decreased risk for obese patients.

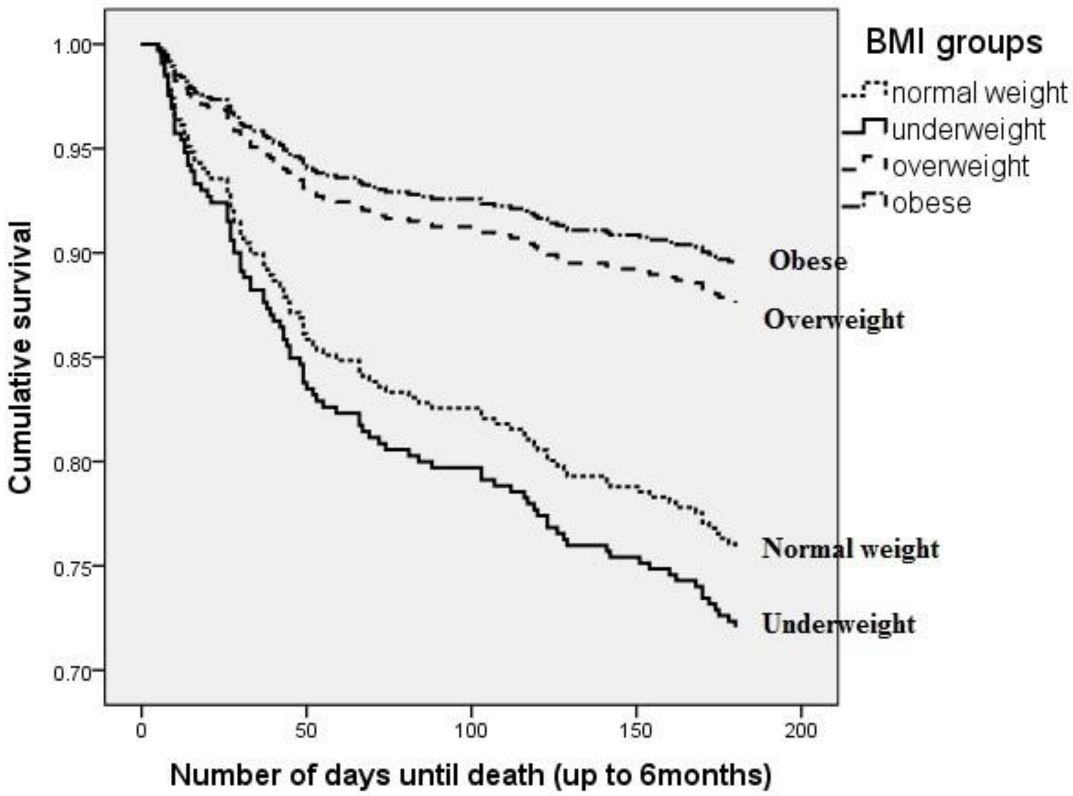


Fig. 4.4 - Survival curves after stroke according to groups of BMI (univariate analysis).

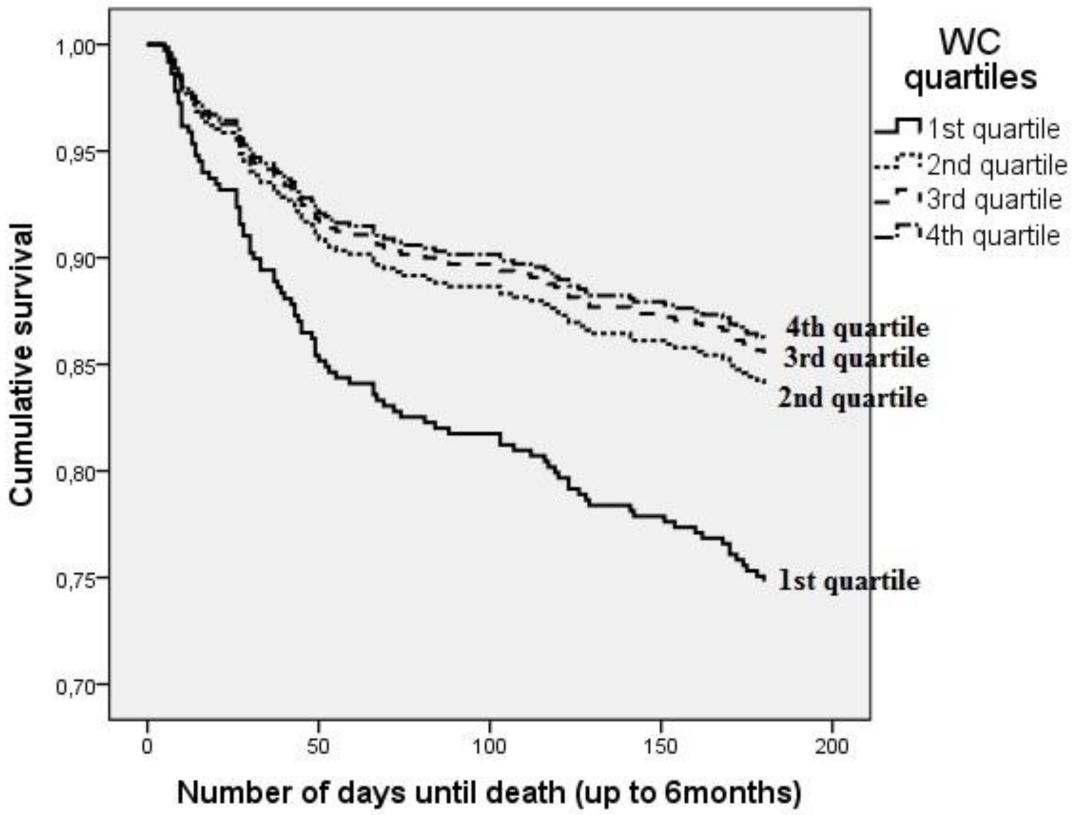


Fig. 4.5 - Survival curves after stroke according to (gender specific) quartiles of WC (univariate analysis).

A similar analysis was conducted to study the association between risk of malnutrition and 6-month mortality, which proved to be statistically significant and graded: the greater the risk of malnutrition, the higher the rate of mortality (*$p<0.001$* for both NST), and the higher the unadjusted (*$p<0.001$* for both NST) and adjusted risk of mortality (*$p<0.001$* for both NST) – see table 4.4 and figures 4.6 and 4.7. Further information regarding the effect of different variables on 6-month mortality can be found in appendix 4.11 c) and d).

Table 4.4 - Rates of mortality and risk of mortality according to nutrition risk category, using univariate and multivariable Cox Proportional Hazards Models

	n	Mortality rates	Univariate Cox Proportional Hazards Model		Multivariable [a] Cox Proportional Hazards Model	
		(Chi-square test)	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Guy's and St. Thomas' Nutrition Screening Tool	543	*p<0.001*	*p<0.001*		*p<0.001*	
Low risk	320	5.3%	Reference group		Reference group	
Medium risk	52	13.5%	2.7	1.10-6.40	2.1	0.87-5.09
High risk	171	41.5%	10.2	6.01-17.34	5.99	3.42-10.50
Malnutrition Universal Screening Tool	537	*p<0.001*	*p<0.001*		*p<0.001*	
Low risk	342	5.8%	Reference group		Reference group	
Medium risk	39	25.6%	4.89	2.29-10.45	3.77	1.71-8.31
High risk	156	41.7%	9.27	5.61-15.30	5.58	3.24-9.64

[a] - *results adjusted for the effect of age, gender, ethnicity, type of stroke, severity of stroke and stroke risk factors (hypertension, diabetes, dyslipidemia, smoking, IHD, heart failure, atrial fibrillation, previous TIA and heavy alcohol consumption)*

When compared to the reference group (low risk of malnutrition), patients at high risk of malnutrition had an approximately 6-fold increased risk of death, using both NST. At 6 months after stroke, less than 6% of patients at low risk of malnutrition were dead while more than 40% were dead in the group at high risk of malnutrition.

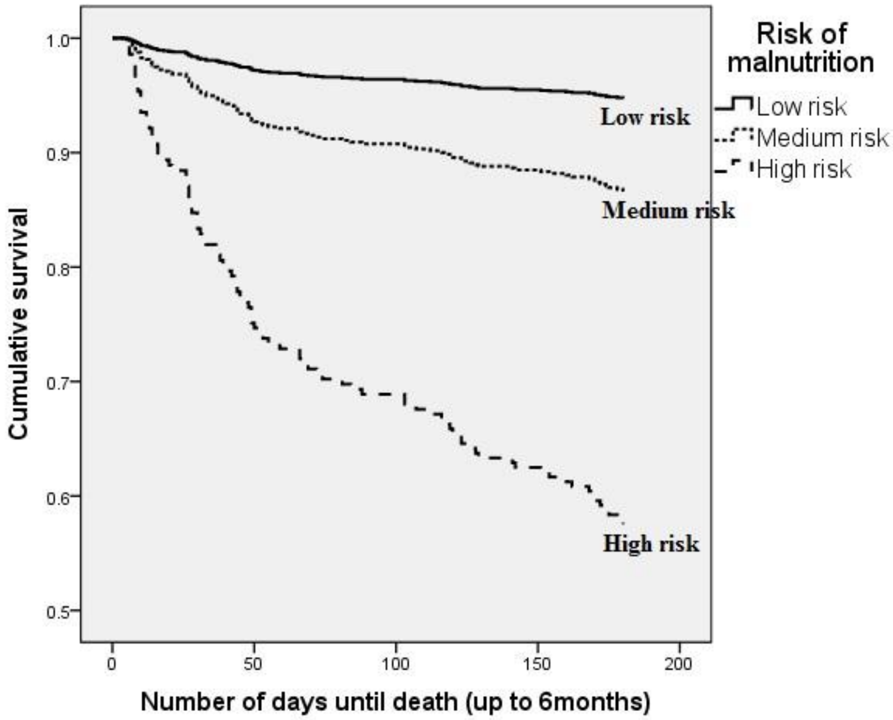


Fig. 4.6 - Survival curves after stroke according to risk of malnutrition (GSTT NST)

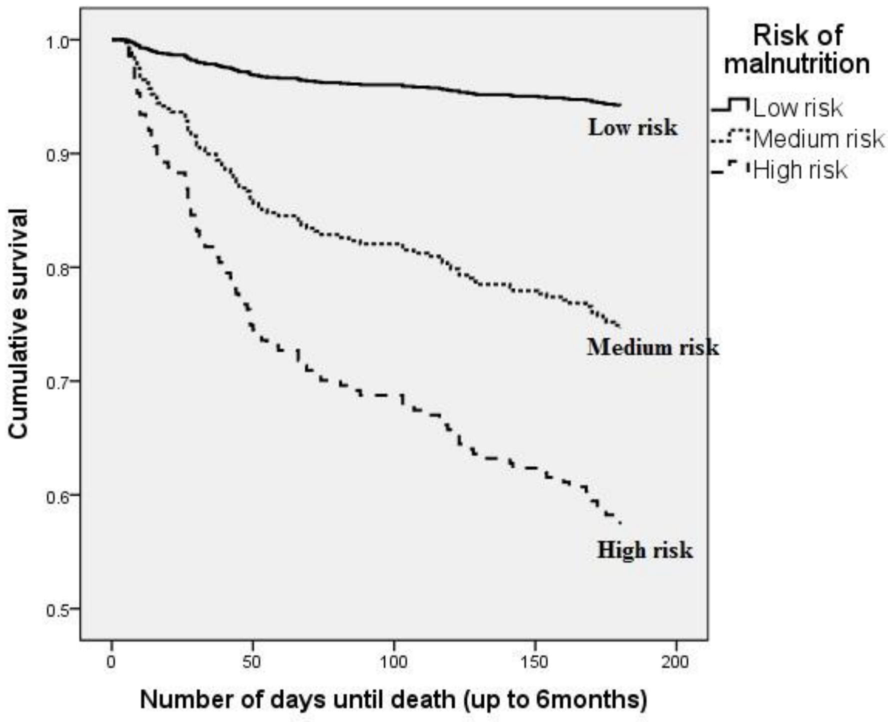


Fig. 4.7 - Survival curves after stroke according to risk of malnutrition (MUST)

Further analyses with subgroups and using BMI as a continuous variable

In order to remove the heterogeneity related to stroke subtype and age, the same statistical analyses were conducted for the subgroup of ischaemic strokes (n=472) and for the subgroup of patients aged 65 and older (n=434)

Similar results were observed: the higher the BMI, the lower the risk of mortality, and there was a non significant trend for a lower risk of death in patients with greater WC. Risk of malnutrition continued to have an important prognostic value, where the higher the risk of malnutrition, the higher the risk of mortality. Details regarding these data can be found in appendices 4.12, 4.13, 4.14 and 4.15.

However, these results should be interpreted with caution due to the relatively small sample size of each group.

It was also investigated whether the relationship between BMI and mortality is linear or quadratic. Multivariable Cox regression models were performed using BMI as a continuous variable and taking into consideration the effect of age, ethnicity, severity of stroke, gender, type of stroke and stroke risk factors, suggesting that there is no linear (p= 0.163) or quadratic (p=0.254) relationship between BMI and mortality.

b) Length of hospital stay

Distribution of LOS was analysed with histograms and Q-Q plots. Data were tested for normality and, as anticipated from the literature, they were not normally distributed (Kolmogorov-Smirnov test, $p<0.001$).
LOS data were log-transformed and tests for normality were repeated, showing that the log-transformed LOS was also not normally distributed (Kolmogorov-Smirnov test, $p=0.001$). Therefore, non-parametric tests were used to explore differences on LOS between patients in the 3 malnutrition risk categories.

As shown in table 4.5, the distribution of LOS was significantly different across nutrition risk categories (Kruskal-Wallis test, $p<0.001$, for both NST), and this association remained significant after taking into account the effects of age, gender, ethnicity, type and severity of stroke, using univariate analysis of variance on ranked data ($p<0.001$, for both NST). Furthermore, adding stroke risk factors to the model did not alter the significant association between nutrition risk category and LOS ($p<0.001$) – appendix 4.16 a) and b).
LOS increased progressively with malnutrition risk category, from a median of 14 to 48 days.

Figure 4.8 illustrate a clear graded association between nutrition risk category and LOS (data taken from table 4.5). For those who survived, the median number of days spent in hospital in a period of 6 months was at least 2 times higher for patients who were at high risk of malnutrition.

Table 4.5 – Length of hospital stay in patients who survived a 6 months, according to risk of malnutrition (unadjusted and adjusted results)

		n (%)	Median number of days	Min-Max	Kruskal-Wallis test (p-value)	Univariate analysis of variance [a] (p values)
GSTT NST (n=448)	**Low risk**	303 (68%	14	2-173	<0.001	<0.001
	Medium risk	45 (10%)	27	2-161		
	High risk	100 (22%)	48	2-194		
MUST (n=442)	**Low risk**	322 (73%)	14	2-173	<0.001	<0.001
	Medium risk	29 (7%)	19	3-165		
	High risk	91(20%)	48	2-194		

[a] - *analysis of ranked LOS and adjusted for the effect of age, gender, ethnicity, type and severity of stroke*
GSTT NST = Guy's and St. Thomas' Nutrition Screening Tool
MUST = Malnutrition Universal Screening Tool

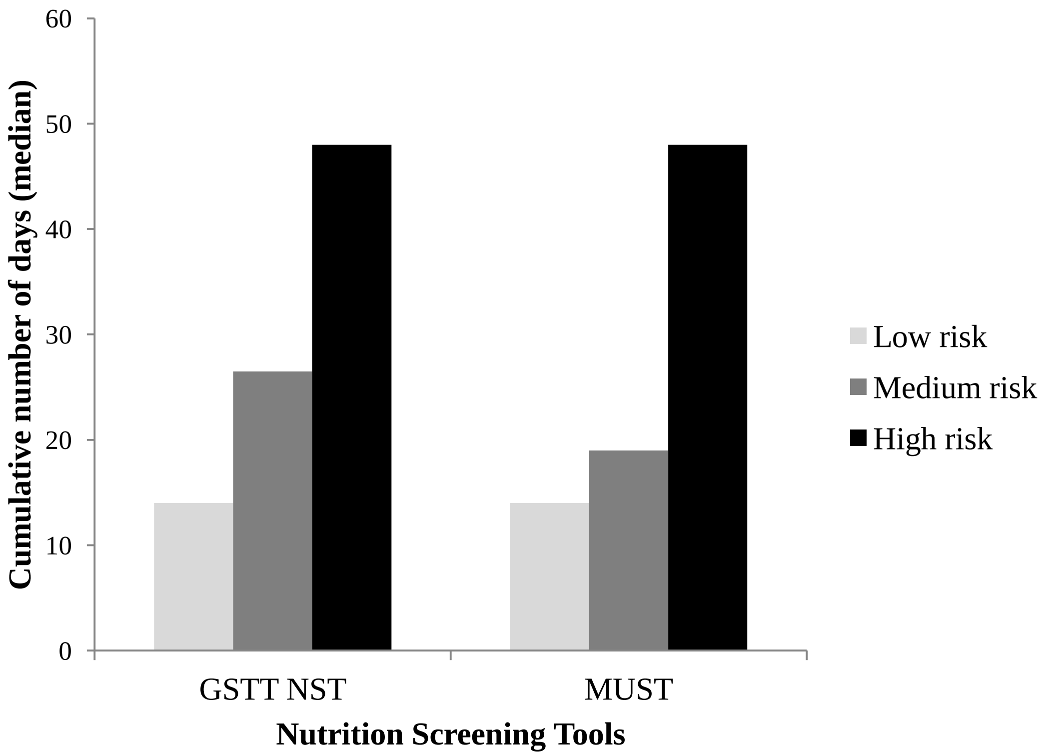


Fig. 4.8 – Median number of days in each category of risk of malnutrition

GSTT NST = Guy's and St. Thomas' Nutrition Screening Tool
MUST = Malnutrition Universal Screening Tool

Similar analyses were conducted for groups of BMI and WC, showing that there were no statistically significant differences in LOS between patients in the 4 categories of BMI (*p=0.348*) and WC (*p=0.655*) – appendix 4.17.

c) Costs of hospitalisation

2% of the HRG codes provided by HES were not valid or there are no published tariffs for these codes and, therefore, admissions or episodes linked to these codes were excluded. The 35 patients who had one admission with an invalid code or a code with no published tariff were identified, to allow for a sensitivity analysis, which was later conducted. From these, 2 patients had costs equal to zero because the excluded admission was the only admission that they had. As a result, these 2 patients were excluded from the cost analyses otherwise their null cost would be incorrectly taken into account.

Distribution of hospitalisation costs was analysed with histograms and Q-Q plots. Data were tested for normality and they were not normally distributed (Kolmogorov-Smirnov test, $p<0.001$).

Hospitalisation costs data were log- and square-root transformed and tests for normality were repeated, showing that the transformed data were not normally distributed (Kolmogorov-Smirnov test, $p=0.001$). Therefore, non-parametric tests were used to explore differences in costs of hospitalisation at 6 months post stroke between surviving patients in the 3 malnutrition risk categories.

Table 4.6 demonstrates that the costs of hospitalisation were significantly different across nutrition risk categories (Kruskal-Wallis test, $p<0.001$ for GSTT NST and $p=0.049$ for MUST), and this association remained significant after taking in consideration the effect of age, gender, ethnicity, type and severity of stroke, using univariate analysis of variance on ranked data ($p<0.001$, for both NST). Age, severity and type of stroke were also significant predictors of hospitalisation costs ($p<0.05$, in both models). Furthermore, adding the stroke risk factors to the model did not alter the significant association between risk of malnutrition and costs of hospitalisation ($p<0.001$) - appendix 4.18 a) and b).

Costs increased progressively with malnutrition risk category, from a median of less than £5000 in patients at low risk of malnutrition to more than £8000 in patients at high risk of malnutrition. When compared to individuals at low risk of malnutrition as classified by the GSTT NST, the median cost of hospitalisation was 80% higher for individuals at high risk of malnutrition and 27% higher for those at medium risk.

Figures 4.9 and 4.10 illustrate a clear graded association between risk of malnutrition and costs of hospitalisation (data taken from table 4.6).

Table 4.6 – Hospitalisation costs of patients at 6 months post-stroke, according to risk of malnutrition

		n	**Median £ (min-max)**	**Kruskal-Wallis test (p-value)**	**Univariate analysis of variance [a] (p values)**
GSTT NST (n=446)	**low risk**	301	**4865** (437-38245)	<0.001	0.001
	medium risk	45	**6928** (715-26147)		
	high risk	100	**8777** (552-31905)		
MUST (n=440)	**low risk**	320	**4917.5** (437-38245)	0.049	0.001
	medium risk	29	**6488** (1052-19596)		
	high risk	91	**8717** (552-31905)		

[a] - *results on ranked hospitalisation costs and adjusted for the effect of age, gender, ethnicity, type and severity of stroke*
GSTT NST = Guy's and St. Thomas' Nutrition Screening Tool
MUST = Malnutrition Universal Screening Tool

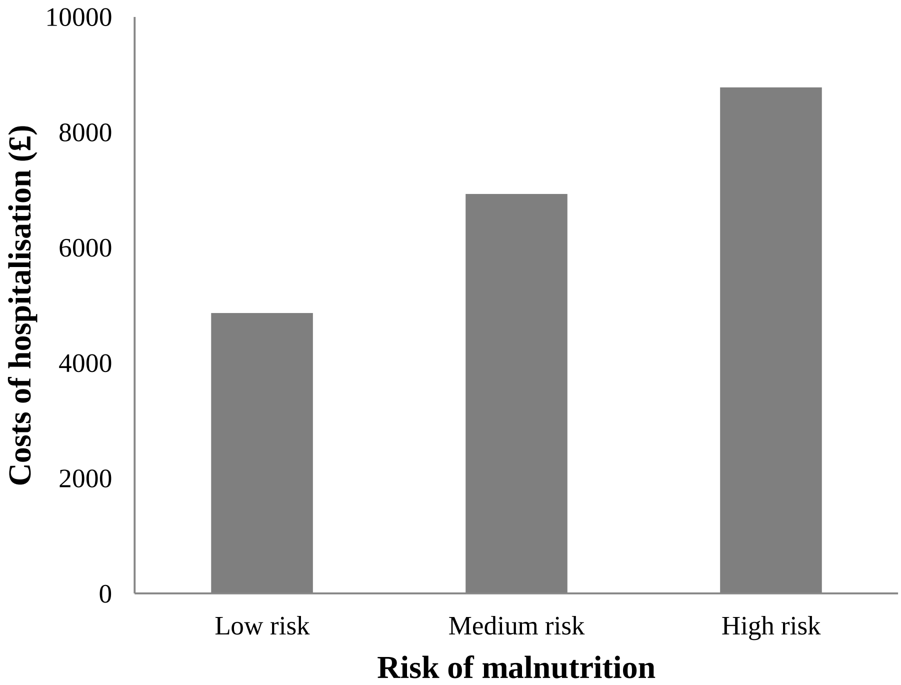


Fig. 4.9 – Median hospitalisation costs of patients at 6 months post-stroke, according to risk of malnutrition as determined by the GSTT NST

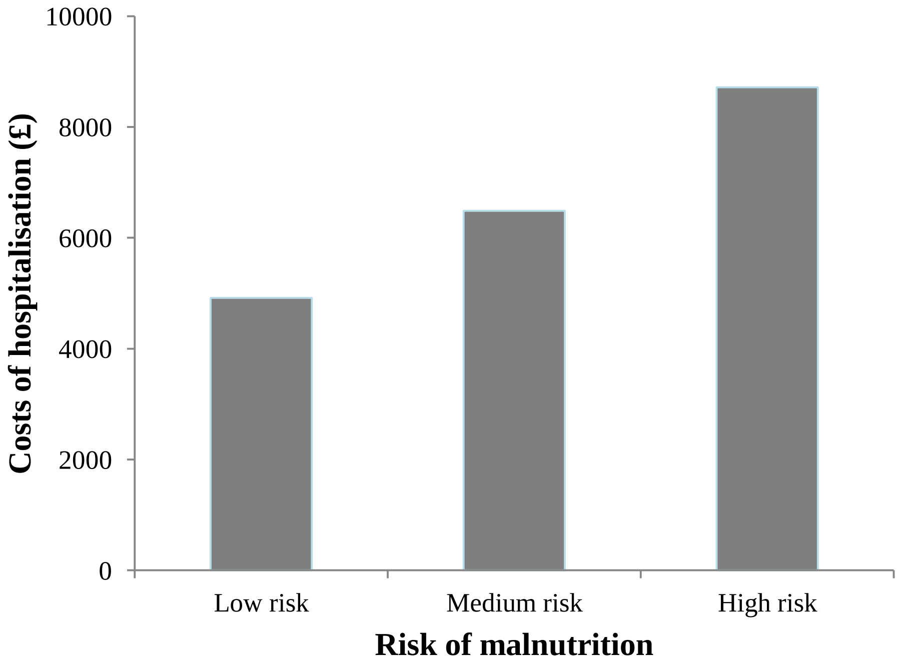


Fig. 4.10 – Hospitalisation costs of patients at 6 months post-stroke, according to risk of malnutrition as determined by the MUST

Similar analyses were conducted for groups of BMI and WC, and there were no statistically significant differences in hospitalisation costs between patients in the 4 categories of BMI (*p=0.729*) and WC (*p=0.713*). However, obese individuals presented the lowest costs (median of £5260) of all BMI groups, and those who were underweight posed the highest economic burden (median of £7544) – see appendix 4.19.

A sensitivity analysis was carried out to understand the impact of removing 2% of the admission data, due to lack of information on costs. Analysis was repeated without the 35 patients who had an excluded admission and the associations between risk of malnutrition and hospitalisation costs previously observed remained significant and in the same direction.

d) Hospital readmissions

Patients who survived and were readmitted to hospital during a period of 6 months post-stroke were identified. The analyses showed that there were no statistically significant differences between rates of hospital readmissions for patients in the 3 malnutrition risk categories, although there was a (non significant) trend for a higher percentage of hospital readmissions in patients at medium and high risk of malnutrition (table 4.7 and fig. 4.11).

Table 4.7 – Percentage of patients readmitted to hospital at 6 months post-stroke, according to risk of malnutrition

		n	Percentage of patients readmitted to hospital	Chi-square test (p value)
GSTT NST (n=448)	**Low risk**	303	58.7%	0.233
	Medium risk	45	64.4%	
	High risk	100	68.0%	
MUST (n=442)	**Low risk**	322	59.0%	0.287
	Medium risk	29	62.1%	
	High risk	91	68.1%	

GSTT NST = Guy's and St. Thomas' Nutrition Screening Tool
MUST = Malnutrition Universal Screening Tool

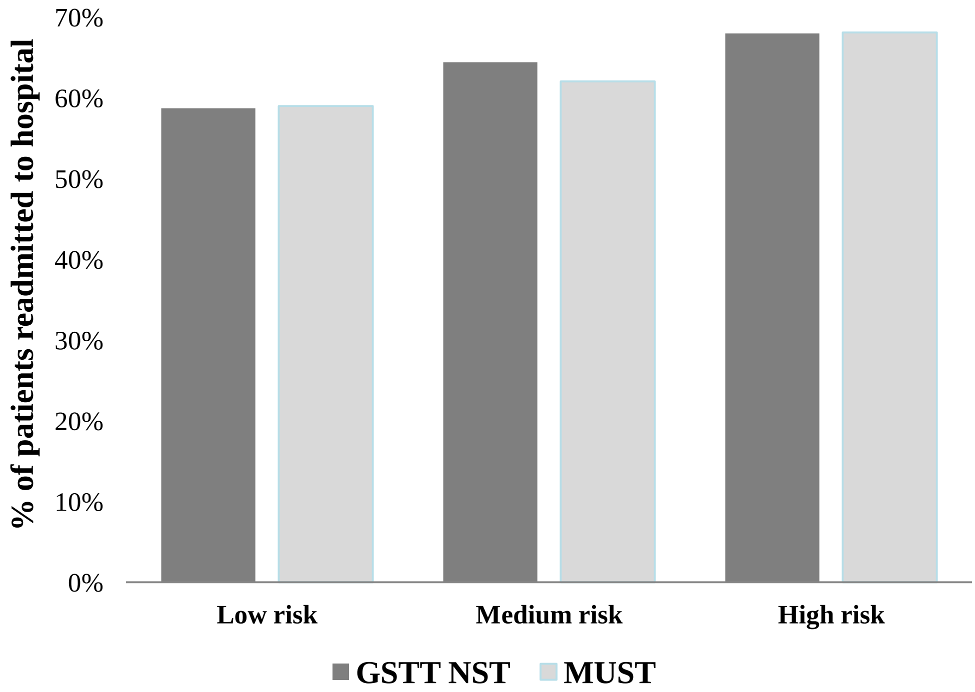


Fig 4.11 – Percentage of patients readmitted to hospital at 6 months post-stroke, according to risk of malnutrition (data taken from table 4.7).

GSTT NST = Guy's and St. Thomas' Nutrition Screening Tool
MUST = Malnutrition Universal Screening Tool

Similar analyses were conducted for groups of BMI and WC, showing that there were no statistically significant differences in the proportion of patients readmitted to hospital at 6 months post-stroke between the 4 categories of BMI (*p=0.984*) or WC (*p=0.288*).

Given that the median number of hospital readmissions for the sample of patients who survived at 6 months was 1, data were also divided into 2 groups, i.e. group of patients who had 1 or no hospital readmissions and group of patients who had 2 or more hospital readmissions. Chi-square tests demonstrated, once again, that there were no significant differences across GSTT NST categories (*p=0.120*), MUST categories (*p=0.266*), BMI categories (*p=0.575*) and WC quartiles (*p=0.681*).

e) Stroke recurrence

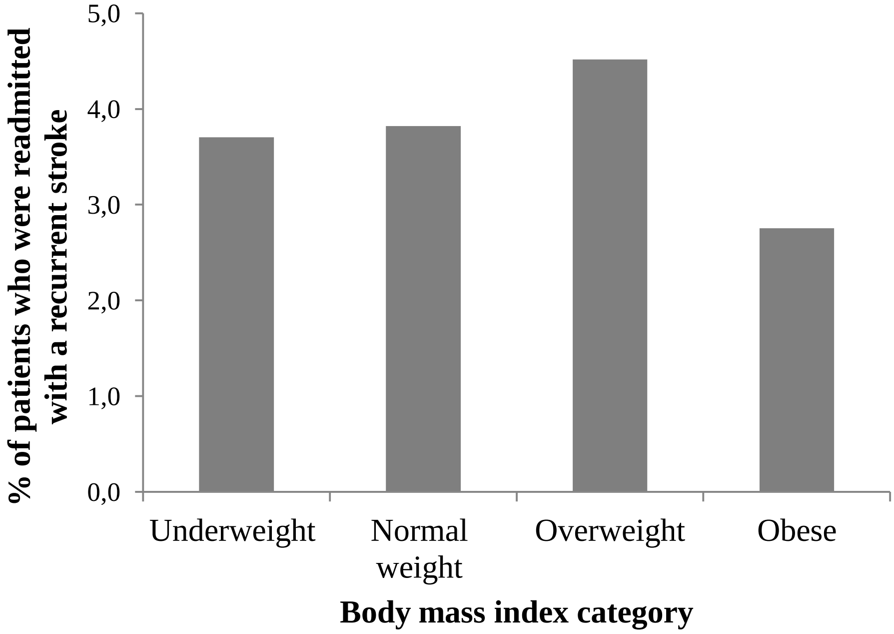
Stroke recurrence (n=17 cases) was identified from the diagnoses at hospital readmissions, during a period of 6 months, for those patients who survived. Excluding patients who died guarantees the exclusion of false negatives (i.e. a patient who died does not count as a patient who did not have a recurrent stroke).

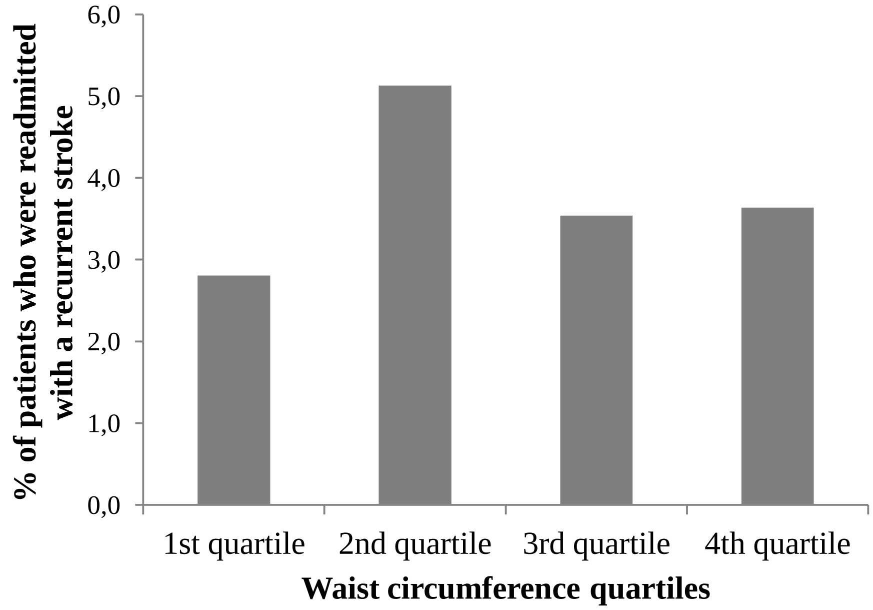
No statistically significant differences were found in stroke recurrence for patients who survived at 6 months, across BMI (*p=0.909*) and WC (*p=0.829*) groups. Surprisingly, obese patients were the group with the lowest rate of stroke recurrence (2.8 %) (see table 4.8 and figures 4.12 and 4.13).

Table. 4.8 - Percentage of surviving patients who were readmitted with a recurrent stroke at 6 months after admission, according to BMI and WC categories

		n	Percentage of recurrent strokes	Chi-square test (p value)
Body mass index (n=448)	**Underweight**	27	3.7	0.909
	Normal weight	157	3.8	
	Overweight	155	4.5	
	Obese	109	2.8	
Waist circumference quartiles (n=447)	**1st quartile**	107	2.8	0.829
	2nd quartile	117	5.1	
	3rd quartile	113	3.5	
	4th quartile	110	3.6	

Fig 4.12 and fig. 4.13 - Percentage of surviving patients who were readmitted with a recurrent stroke at 6 months after admission, according to BMI and WC categories





Similar analyses were conducted for both NST, showing that there were no statistically significant differences in stroke recurrence rates between patients in the 3 malnutrition risk categories (*p=0.883* for GSTT NST and *p=0.531* for MUST).

Given that some patients may have been readmitted to hospital with a diagnosis of a recurrent stroke and may have died within 6 months post stroke, previous analyses were repeated taking into consideration all patients (i.e. without excluding those who had died at 6 months). The number of patients with a recurrent event rose to 24. Nevertheless, results were identical, with no significant differences across BMI (*p=0.877*), WC (*p=0.357*), GSTT NST (*p=0.500*) and MUST categories (*p=0.714*).

f) Comparison of the two NST with regards to their performance to predict post-stroke outcomes

Both NST were compared for their ability to predict mortality, hospital stay and hospitalisation costs by using ROC curves (Zweig and Campbell, 1993). The ROC curves analyses of LOS and hospitalisation costs excluded the patients who died during the follow-up period.
LOS and hospitalisation costs were classified into 2 groups: short LOS (≤ 18 days) and long LOS (> 18 days), as well as low (≤ £5890) and high hospitalisation costs (> £5890), using the median of the variables distribution as a cut-off point.

The ROC curves obtained for each outcome are displayed in figure 4.14, and the areas under the ROC curves values for each outcome are summarised in table 4.9.

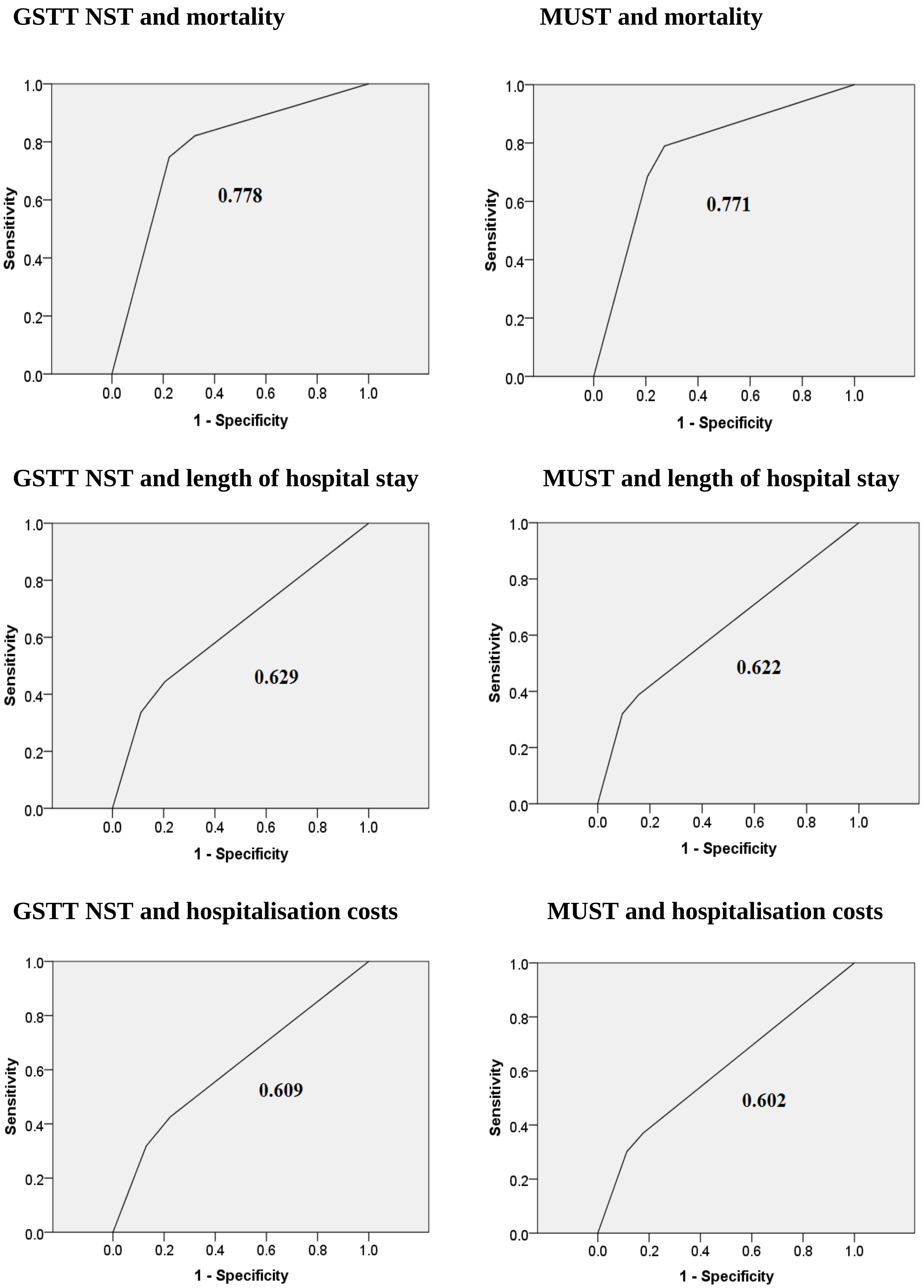


Fig 4.14 – ROC curves of GSTT NST and MUST for mortality, length of hospital stay and hospitalisation costs.

ROC = receiver operating characteristic, GSTT NST = Guy's and St. Thomas' Nutrition Screening Tool, MUST = Malnutrition Universal Screening Tool

Table 4.9 – Area under ROC curves values of the nutrition screening tools for each outcome

Nutrition screening tool	**Outcome**		
	Death	**Length of hospital stay**	**Hospitalisation costs**
GSTT NST	0.778	0.629	0.609
MUST	0.771	0.622	0.602

GSTT NST = Guy's and St. Thomas' Nutrition Screening Tool
MUST = Malnutrition Universal Screening Tool
ROC = receiver operating characteristic

The values of the areas under the ROC curves demonstrate that the screening tools have a fair accuracy, and the most effective tool in predicting outcomes is the one with the largest area under the ROC curve.

For each outcome, the GSTT NST presented slightly higher values than MUST. Thus, GSTT NST has a slightly better predictive value, although it can be concluded that the ability of both tools to predict negative outcomes is similar.

Given the interesting prognostic value of the NSTs, it was further investigated:

g) the characteristics of patients at high risk of malnutrition

The characteristics believed to be related with risk of malnutrition are shown on the following tables (tables 4.10 and 4.11). Differences between groups were analysed using Chi-square tests for categorical variables and ANOVA for continuous variables.

Table 4.10 – Characteristics of patients according to risk of malnutrition, as defined by the GSTT NST

	Low risk	Medium risk	High risk	p value
Age, mean in years (SD)	72.5 (13.9)	73.8 (13.4)	79.2 (12.2)	<0.001
Range (minimum-maximum)	22 - 95	30 - 98	25 - 99	
NIHSS score, mean (SD)	6.2 (4.9)	6.5 (4.5)	10.7 (6.3)	<0.001
Range (minimum-maximum)	0-27	1-20	0-25	
Gender, n				0.142
Male, n (%)	175 (55)	23 (44)	80 (47)	
Female, n (%)	145 (45)	29 (56)	91 (53)	
Type of stroke, n				0.073
Ischaemic, n (%)	280 (87)	49 (94)	143 (84)	
Haemorrhagic, n (%)	38 (12)	2 (4)	28 (16)	
Subarachnoid haemorrhage, n (%)	2 (1)	1 (2)	0	
Living conditions prior to stroke				0.015
Home (unsupported), n (%)	77 (24)	13 (15)	5 (32)	
Home (with support), n (%)	238 (74)	38 (73)	111 (65)	
Institutionalized (care home), n (%)	5 (2)	0	5 (3)	
Other, n (%)	0	1 (2)	0	
Chronic conditions related to malnutrition				
Gastrointestinal diseases, n (%)	26 (8)	4 (7)	22 (13)	0.209
Cognitive dysfunction, n (%)	18 (6)	2 (4)	17 (10)	0.131
Impaired mobility, n (%)	22 (7)	7 (14)	33 (19)	<0.001
Had a previous stroke	65 (20)	11 (21)	43 (25)	0.463
Failed swallow screening test	63 (20)	11 (21)	111 (65)	<0.001

Numbers in parentheses indicate percentages for categorical data and SD (standard deviation) for continuous data; NIHSS = National Institutes of Health Stroke Scale

Patients at high risk of malnutrition, as defined by the GSTT NST, were more likely to be older, to have a more severe stroke, to live at home with no support, to have impaired mobility (prior to stroke) and to fail the swallow screening test.

Table 4.11 – Characteristics of patients according to risk of malnutrition, as defined by the MUST

	Low risk	Medium Risk	High risk	p value
Age, mean in years (SD)	72.4 (14.1)	78.1 (13.7)	78.9 (12.7)	<0.001
Range (minimum-maximum)	22 - 98	35 - 94	25 - 99	
NIHSS score, mean (SD)	6.2 (4.8)	5.7 (3.8)	11.3 (6.3)	<0.001
Range (minimum-maximum)	0-27	1-18	0-25	
Gender, n				0.101
Male, n (%)	181(53)	24 (61)	70 (45)	
Female, n (%)	161 (47)	15 (39)	86 (55)	
Type of stroke, n				0.001
Ischaemic, n (%)	303 (89)	32 (82)	132 (85)	
Haemorrhagic, n (%)	38 (11)	5 (13)	24 (15)	
Subarachnoid haemorrhage, n (%)	1 (0.3)	2 (5)	0	
Living conditions prior to stroke				0.005
Home (unsupported), n (%)	81 (24)	10 (26)	51 (33)	
Home (with support), n (%)	255 (74)	28 (72)	101 (65)	
Institutionalized (care home), n (%)	6 (2)	0	4 (2)	
Other, n (%)	0	1 (2)	0	
Chronic conditions related to malnutrition				
Gastrointestinal diseases, n (%)	27 (8)	2 (5)	22 (14)	0.057
Cognitive dysfunction, n (%)	22 (6)	2 (5)	12 (8)	0.803
Impaired mobility, n (%)	28 (8)	3(8)	30 (19)	0.001
Had a previous stroke	71 (21)	8 (21)	38 (24)	0.652
Failed swallow screening test	64 (19)	10 (26)	110 (61)	<0.001

Numbers in parentheses indicate percentages for categorical data and SD (standard deviation) for continuous data; NIHSS = National Institutes of Health Stroke Scale

Patients at high risk of malnutrition, as defined by the MUST, were more likely to be older, to have a more severe stroke, to have a haemorrhagic stroke, to live at home with no support, to have a gastrointestinal disease, to have impaired mobility (prior to stroke) and to fail the swallow screening test.

h) Mortality, LOS and hospitalisation costs for patients who unintentionally lost weight before stroke

Knowing that the nutritional status of an individual who suffered a stroke can deteriorate as a consequence of the event (due to dysphagia, decreased alertness, physical impairment, etc., as previously discussed), the independent impact of unintentional weight loss prior to stroke (as an indicator of a poor nutritional status) on stroke outcomes was also investigated, at 6 months after admission.

It was observed that 110 out of 543 patients (20%) unintentionally lost weight 3 to 6 months before hospital admission. Patients were classified into different groups of unintentional weight loss according to the criteria used in both NST. Thus, there were 2 groups for GSTT NST (“yes” or “no”) and 3 groups for MUST (“<5%”, “5-10%” and “>10%”).

The Chi-square test was used to compare rates of mortality, and Cox Proportional Hazards Models were used to compare risk of mortality (crude and adjusted HR) between groups with (and without) unplanned weight loss. Results are summarized in the following tables and figures (table 4.12 and figures 4.15 and 4.16), showing that patients who lost weight had a higher rate of mortality ($p<0.001$ for GSTT NST), and the higher the % of weight loss, the higher the rate of mortality ($p<0.001$ for MUST).
The unadjusted ($p<0.001$ for both NST) and adjusted risk of mortality ($p=0.005$ *for GSTT NST and* $p=0.001$ for MUST) was also significantly higher for individuals who had an unintentional weight loss prior to hospital admission for stroke.

Table 4.12 - Rates of mortality and risk of mortality according to groups of unintentional weight loss, using univariate and multivariable Cox Proportional Hazards Models

Method used to classify unintentional weight loss	**n**	**Mortality rates (Chi-square test)**	**Univariate Cox Proportional Hazards Model**		**Multivariable [a] Cox Proportional Hazards Model**	
			Hazard Ratio	**95% CI**	**Hazard Ratio**	**95% CI**
Guy's and St. Thomas' Nutrition Screening Tool	543	*p<0.001*	*p<0.001*		*p=0.005*	
No	433	14.3%	Reference group		Reference group	
Yes	110	30.0%	2.33	1.53-3.56	1.87	1.21-2.91
Malnutrition Universal Screening Tool	537	*p<0.001*	*p<0.001*		*p=0.001*	
<5%	445	13.9%	Reference group		Reference group	
5-10%	43	30.2%	2.43	1.34-4.42	1.75	0.95-3.25
>10%	49	40.8%	3.48	2.10-5.76	2.68	1.55-4.63

[a] - *results adjusted for the effect of age, gender, ethnicity, type of stroke, severity of stroke and stroke risk factors (hypertension, diabetes, dyslipidemia, smoking, IHD, heart failure, atrial fibrillation, previous TIA and heavy alcohol consumption)*

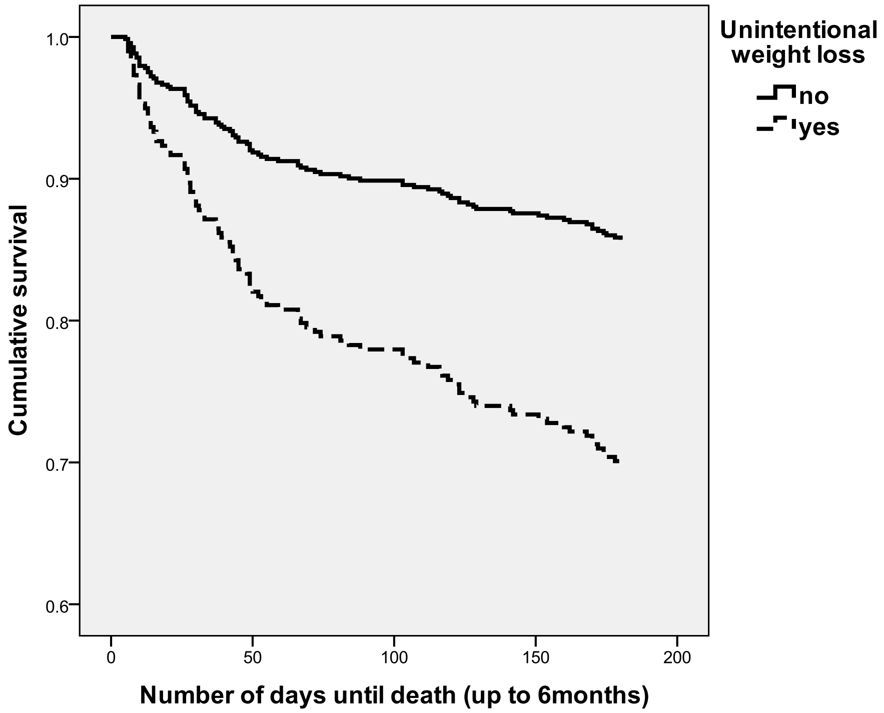


Fig. 4.15 - Survival curves after stroke according to groups of unintentional weight loss (as classified by GSTT NST)

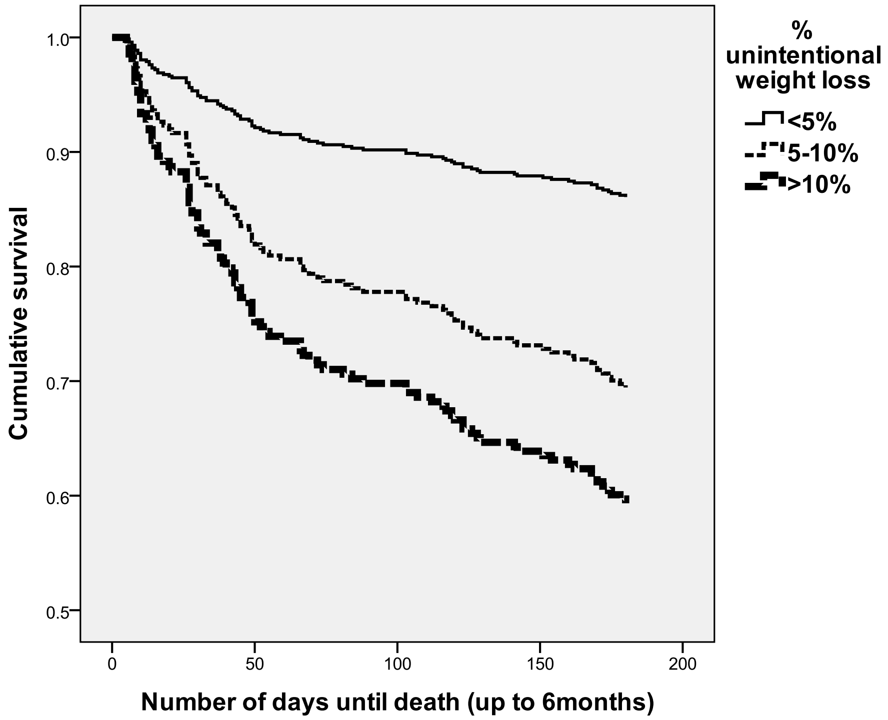


Fig. 4.16 - Survival curves after stroke according to groups of unintentional weight loss (as classified by MUST)

Tables 4.13 and 4.14 summarise the differences on LOS and hospitalisation costs in patients who survived at 6 months, according to groups of unintentional weight loss.

According to the GSTT NST, individuals who unintentionally lost weight prior to admission had a statistically significant longer LOS (p=0.004) and higher cost of hospitalisation (p=0.03) than those who did not (lose weight), and this association remained significant after taking into consideration the effect of age, gender, ethnicity, type and severity of stroke, using univariate analysis of variance on ranked data (*p*=0.002 for LOS and p=0.017 for hospitalisation costs).

According to MUST, the higher the percentage of weight loss prior to stroke, the longer the LOS and the higher the hospitalisation costs at 6 months post stroke. This association was significant for LOS, before (p=0.019) and after (p=0.016) the adjustment for possible confounders, and there was a trend for significant association between percentage of unintentional weight loss and hospitalisation costs (p=0.066 for the unadjusted results and p=0.054 for the adjusted results).

LOS increased progressively with the increase in percentage unintentional weight loss, from a median of 17 to 40 days, and the same pattern was observed for costs, starting with a median of £5506 in patients who had no unintentional weight loss (or less than 5%) to a median of £8416 for individuals who lost more than 10% of their usual weight prior to hospital admission for stroke.

Table 4.13 - Length of hospital stay of patients who survived 6 months, according to groups of unintentional weight loss (unadjusted and adjusted results)

Method used to classify unintentional weight loss		n	Median number of days	Min-Max	Mann-Whitney / Kruskal-Wallis tests (p-value)	Univariate analysis of variance [a] (p values)
GSTT NST (n=448)	**No**	371	17	2-194	0.004	0.002
	Yes	77	37	2-119		
MUST (n=442)	**<5%**	383	17	2-194	0.019	0.016
	5-10%	30	32	2-102		
	>10%	29	40	2-119		

[a] *- analysis of ranked LOS and adjusted for the effect of age, gender, ethnicity, type and severity of stroke*
GSTT NST = Guy's and St. Thomas' Nutrition Screening Tool
MUST = Malnutrition Universal Screening Tool

Table 4.14 - Hospitalisation costs of patients who survived a 6 months, according to groups of unintentional weight loss (unadjusted and adjusted results)

Method used to classify unintentional weight loss		n	Median £ (min-max)	Mann-Whitney / Kruskal-Wallis tests (p value)	Univariate analysis of variance [a] (p values)
GSTT NST (n=446)	**No**	369	**5506** (437-38245)	0.03	0.017
	Yes	77	**8416** (552-21230)		
MUST (n=440)	**<5%**	381	**5506** (437-38245)	0.066	0.054
	5-10%	30	**6708** (4208-19596)		
	>10%	29	**8416** (552-21230)		

[a] *- analysis of ranked hospitalisation costs and adjusted for the effect of age, gender, ethnicity, type and severity of stroke*
GSTT NST = Guy's and St. Thomas' Nutrition Screening Tool
MUST = Malnutrition Universal Screening Tool

Although it was not the aim of this study to explore the reasons for the observed unintentional weight loss prior to stroke that affected 20 % of recruited patients, whenever possible the author collected this information, from multiple sources, including testimonials from all patients who lost weight, their relatives or carers and medical notes. Reasons for weight loss were then grouped into "disease-related" and "psychological/social", and details can be found in appendix 4.20 (note that this is the original information, as reported by patients, relatives/carers and medical notes).

4.5 - Discussion

The aims of this study were to:

A. determine the ability of MUST to independently predict negative outcomes in acute stroke patients, specifically mortality, LOS, readmissions and hospitalisation costs at 6 months post stroke.

B. determine whether the MUST or GSTT NST is the most effective NST in predicting negative outcomes in patients at 6 months post stroke.

C. determine the association between BMI, central obesity and outcomes (i.e. mortality and recurrent stroke) at 6 months post-stroke.

Aims A. and B.

Regarding the first and second aims, it was observed that both NSTs can be used to predict risk of negative outcomes in stroke patients. Patients at high risk of malnutrition had a significantly higher risk of mortality, a longer LOS and greater costs of hospitalisation at 6 months post stroke. Furthermore, the association between risk of malnutrition and the outcomes was statistically significant and graded: the greater the risk of malnutrition, the higher the risk of mortality, the longer the LOS and the greater the costs.

The results of the ROC curves showed that the ability of both tools to predict negative outcomes was similar. However, MUST had the disadvantage of not being able to be applied to the entire study population, as it was impossible to quantify weight loss in 6 patients (out of 543).

These results are consistent with previous studies conducted in other populations.

In 2006, the MUST was applied to 150 consecutively admitted elderly patients, with a mean age of 85 years and a wide range of conditions (Stratton et al., 2006). The % of patients identified at high risk of malnutrition (41%) was greater than in the present study (30%), but the results were identical in terms of in-hospital mortality and LOS, as both rose significantly with increasing malnutrition risk category.

In a recent study conducted in Singapore (Lim et al., 2012), 818 patients admitted to 16 different wards had their nutritional status assessed by the Subjective Global Assessment (an assessment tool that takes into account information about weight changes, dietary intake, gastrointestinal symptoms, functional capacity, disease, subcutaneous fat, muscle wasting, oedema and ascites (Detsky et al., 1987)). Similar to the findings of the current study, malnutrition affected 29% of patients aged 18-74 years and was an independent predictor of mortality, LOS and hospitalisation costs. Looking at the example of mortality, in the Singapore-based study, malnutrition posed a 4-fold increased risk of death at 1-year follow-up, and in the London-based (present) study, patients at high risk of malnutrition had an approximately 6-fold increased risk of death at 6-month follow up (in the multivariable models of both NST).

In the present study, costs of hospitalisation of individuals at high risk of malnutrition were 80% higher than the costs of low risk patients. This is a major contributor, when compared with other factors that have the potential to influence hospitalisation costs after stroke. For example, it has been shown that atrial fibrillation increases acute hospitalisation costs by 23.5% (Brueggenjuergen et al., 2007), depression by 63% (Husaini et al., 2013), haemorrhagic strokes by 65% (vs. ischaemic strokes (Gioldasis et al., 2008)), and younger patients (18-44 years old vs. 45-64 years old) by 6% (Wang et al., 2014).

Results of a retrospective cohort study conducted in 709 patients (with a wide range of diseases, selected from 25 Brazilian hospitals), also assessed by the Subjective Global Assessment, showed that malnourished patients (of which 26.3% were moderately or suspected malnourished and 7.9% were severely malnourished) incurred a 61% increase in hospitalisation costs (Correia and Waitzberg, 2003). Malnourished patients also had a significantly increased rate of mortality (12.4% vs. 4.7%) and a longer LOS (mean of 16.7 days vs. 10.1 days) when compared with the well-nourished. It should be noted that the Subjective Global Assessment is a nutritional assessment method, while the present study used nutrition screening methods, which are quicker and easier to apply, not requiring specific training in the area. Other studies that determined the hospitalisation costs of nutritionally vulnerable patients report costs 20% (Amaral et al., 2007) or 36% (Chima et al., 1997) higher, when compared to the costs of well nourished patients .

These different figures are probably related to the methodology used to determine the outcomes (e.g. the majority of these studies only analysed the outcomes related with the first admission, until discharge or death), with the tool used to categorise patients as malnourished or at risk of malnutrition, and also with the type of population (e.g. the LOS of stroke patients may be longer than general medical patients, due to the time required for rehabilitation).

However, the results obtained in all these different studies are consistent.

In the stroke population, a study has been conducted to evaluate the impact of malnutrition (undernutrition), as assessed by the Subjective Global Assessment, on outcomes (mortality and functional capacity) at 1 month after stroke (Davis et al., 2004). This tool identified only 16% of patients as being “undernourished”, which is approximately half of the proportion of patients identified at high risk of malnutrition by MUST or the GSTT. These “undernourished” patients were more likely to die and to have a poor functional outcome at 1 month, but these associations were no longer significant after the adjustment for possible confounders. These results are slightly different from the results obtained in the present study, and this may be due to the differences in sample size (543 vs. 185 patients), follow-up time (6 months vs. 1 month) or the tool used to assess nutritional status (risk) (MUST or GSTT NST vs. subjective global assessment, with the latter being a nutrition assessment tool and having a subjective nature).

As mentioned in chapter 1, other studies have explored the prevalence and consequences of malnutrition after stroke using biochemical parameters, such as albumin, to classify patients as being malnourished (Davalos et al., 1996, Gariballa et al., 1998a, Yoo et al., 2008). However, the limitations of using these parameters in the assessment of nutritional status were already pointed out in section 1.3 (e.g. not being specific to nutritional status) and, in fact, a recent consensus statement of renowned institutions does not propose any specific inflammatory markers for diagnostic purposes of adult malnutrition (White et al., 2012).

In the present study, there was a non-significant trend for a higher percentage of patients to be readmitted to hospital in the medium and high risk categories, similar to results obtained in other populations (Lim et al., 2012, Chima et al., 1997). Although these non significant results do not support the study hypothesis it could be argued that spending more days in hospital (i.e. the length of the hospital admission) is a more meaningful outcome than the number of readmissions (or percentage of patients readmitted), as these can be as short as 1 day.

Characteristics of patients at high risk of malnutrition

When the characteristics of patients at high risk of malnutrition (as defined by the MUST) were examined, it was found that these individuals were more likely to be older and to have a more severe stroke (as demonstrated before, in the stroke and non-stroke population (Yoo et al., 2008, Lim et al., 2012)), to have a haemorrhagic stroke (in line with the findings from a study that showed that undernourishment was significantly more prevalent in haemorrhagic strokes (Choi-Kwon et al., 1998)), to live at home with no support, to have a gastrointestinal disease (as shown before in the non-stroke (hospitalised) population (Chima et al., 1997)), to have impaired mobility (prior to stroke) and to fail the swallow screening test.

There is a complex relationship between malnutrition, age and frailty, as frail patients are likely to be at high risk of malnutrition, to be older, and to have higher NIHSS scores (suggesting that they have more severe strokes). All these factors predict poor outcome.

Outcomes of patients who unintentionally lost weight before stroke

Some of the reasons for unintentional weight loss prior to stroke (which were collected from multiple sources of information) were presented in appendix 4.20. They show that unintentional weight loss is not only associated with a disease/occult pathology or untreated chronic disease such as cancer; instead, it may involve psychological and social reasons such as lack of interest in preparing own food, social isolation and depression due to the death of a close relative. In other words, malnutrition has multi-factorial causes, which need to be explored by health and social care professionals so they can provide effective nutritional interventions.

In the current study approximately 20% of patients had unintentionally lost weight 3 to 6 months before hospital admission and they had a significantly higher risk of mortality, a longer LOS and greater costs of hospitalisation, when compared to patients with no unintentional weight loss. Stratton and her colleagues (Stratton et al., 2006) also observed that weight loss of > 5% prior to admission affected 35% of hospitalised elderly patients and was a good predictor of mortality. Raslan and her colleagues (Raslan et al., 2010) also demonstrated that the 16.2% of hospitalised patients (with a wide range of diseases) who unintentionally lost more than 10% of their weight prior to admission stayed in hospital for a longer period of time. However, in contrast to the current study, LOS was only related with the first admission, excluding any other hospital readmissions within a certain period of time.

In summary, these results show the value of screening for risk of malnutrition (including the question related to unintentional weight loss prior to stroke). MUST and GSTT NST can adequately identify stroke patients who are more likely to suffer worse outcomes and, consequently, those who are more likely to benefit from nutritional interventions.

Furthermore, these tools can be very useful to support hospital administration. If malnourished patients are accurately diagnosed and coded as such, this correctly reflects the resources that the hospitals might spend on them, which can enhance the reimbursement that the hospital receives for the treatment of those patients (Funk and Ayton, 1995).

Treatment costs for stroke account for approximately 5% of total NHS costs in the United Kingdom (Saka et al., 2009), and in the United States of America the total annual costs of stroke are projected to increase to $240.67 billion by 2030, an increase of 129% over the next 2 decades (Ovbiagele et al., 2013). The findings of this thesis show that patients at high risk of malnutrition cost 80% more than those at low risk, demonstrating that malnutrition has a major contribution to this outcome.

Aim C.

BMI, WC and mortality

Regarding the third aim of the study, a significant difference was observed in the rates of mortality between patients across BMI and WC categories, at 6 months post-stroke, with the higher the BMI and the WC quartile, the lower the mortality rates.

BMI was a statistically significant independent risk factor for mortality, both in the univariate and multivariable analysis while the impact of WC was only significant in the univariate analysis, suggesting that WC does not add any predictive value to this outcome.

In the multivariable model, having the normal weight category as a reference group, being overweight was associated with a 43% decreased risk of death and with a 54% decreased risk for obese patients.

These findings of a better survival in overweight/obese patients or those with a larger WC were similar to the analyses conducted in the subgroups of ischaemic strokes or patients aged 64 and older. Although surprising, they are also in line with the results from the present study regarding risk of malnutrition (given that underweight patients had the highest rates of mortality), with the results from previous studies (as discussed in the literature review presented in chapter 3) and with the results from the SLSR data (chapter 3).

The small differences between results in chapter 3 and 4 (e.g. U shaped relationship between BMI and mortality observed in chapter 3, but not in the present study) may be due different characteristics of the populations. The first study included only first strokes, with a mean age of 68.5 +/- 15 years, and a follow-up period of up to 8 years, while the population of the present study included first and recurrent strokes, was older (with a mean age of 74.7 +/- 14 years) and their outcomes were evaluated only at 6 months. Additionally, the amount of missing data regarding the record of BMI were minimal in the present study, in comparison to the 47% observed on the SLSR study, and in the present study there were no missing data regarding covariates (e.g. NIHSS score), preventing patients from being excluded from the multivariable analyses. In the present study, all the data were systematically and consistently collected by only one researcher.

BMI, WC and stroke recurrence

When the second outcome was analysed (stroke recurrence), no significant differences were found on stroke recurrence rates in patients who survived at 6 months, across BMI and WC groups. It was expected that obese patients would experience more readmissions for recurrent stroke but, surprisingly, the rate of stroke recurrence for this group was no higher than for the others.

As mentioned in the introduction of this chapter (section 4.1), a few studies have evaluated the impact of BMI on stroke recurrence:

a) similar to the present findings, a study conducted in 20246 patients older than 55 years with an ischaemic stroke and followed for 2.5 years, showed that being overweight and obese was not associated with increased recurrent stroke (risk), although the reference category was the "lean group" defined by a BMI < 25Kg/m^2 (Ovbiagele et al., 2011).

b) in the same way, in a sub-analysis of an intervention study with 1521 patients who had a stroke or a TIA, recurrent strokes at 2.5 years were non-significantly lower in obese patients (Doehner et al., 2013).

c) the largest study that included this outcome is the Danish Stroke Register, with 29326 patients with a record of BMI who were followed for a similar period of time (mean of 2.6 years). The authors demonstrated that risk of readmission for recurrent stroke was significantly lower in obese patients than in normal weight patients (HR = 0.84 (C.I. 95% 0.72-0.92)) (Andersen and Olsen, 2013).

d) a study with 2785 first-ever stroke patients and with a longer follow-up period (mean of 3.9 years) showed that stroke recurrence was similar among BMI groups. Similarly to Ovbiagele's study, underweight and normal weight patients were combined in one BMI category (< 25Kg/m^2) (Vemmos et al., 2011).

Data from these 4 studies, in conjunction with the present study, suggest that obese stroke patients are not at increased risk of developing a recurrent stroke, and a protective effect of obesity may be observed in larger samples. Nonetheless, the 4 studies described above have limitations that were pointed out in section 4.1.

To the best of the author's knowledge, there are no published data exploring the association between WC (or any other marker of abdominal obesity) in stroke patients and the risk of stroke recurrence. The present study demonstrates that a larger WC is not associated with an increased risk of a recurrent stroke. In fact, patients in the second quartile of WC (91.6-100 cm for men/ 85-94 cm for women) presented the highest rate of stroke recurrence (5.1%), although these results were not statistically significant.

The rationale behind the "obesity paradox"

The biological mechanisms that explain the observed paradoxical associations between BMI, WC and outcomes have not yet been determined.
However, as mentioned before, it was suggested that the ideal BMI for healthy populations may be different from the ideal BMI for populations with a chronic disease (including stroke). It is possible that the fat stores of obese patients make them more resistant to the catabolic progressions of their disease (usually a disease associated with wasting and cachexia, as explained in section 3.1).

Some individuals will struggle to meet their nutrition and hydration requirements post stroke and approximately a quarter of the survivors will have a significant weight loss at 4 months and 1 year post-stroke (Joonsson et al., 2008). As explained in section 1.3 "malnutrition and stroke", there are several factors that can contribute to the deterioration of nutritional status and dehydration post-stroke, such as swallowing and chewing difficulties, motor and sensory impairment, GI dismotility, communication deficits and the poor nutritional composition of MTD (particularly deficient in energy and proteins). In this context, the body fat stores of overweight and obese patients may provide a survival advantage over those who are normal weight or underweight (or those that, even being overweight or obese, unintentionally lose a clinically significant amount of weight prior to stroke).

In a study that aimed to scrutinise the "obesity paradox" in patients with chronic heart failure, it was observed that only obese patients had balanced muscle protein metabolism (i.e. a balance between protein synthesis and degradation) (Aquilani et al., 2012). Clinically, an unbalanced protein metabolism is associated with several comorbidities (e.g. reduced immunological capacity and tissue integrity) (Aquilani et al., 2012). The results of this study may also be extended to patients with a stroke, although research in this population is needed.

It should also be noted that fat tissue has relevant beneficial effects, for example, in the protection against bone fractures (Laet et al., 2005), infectious complications and pressure ulcers (Bouillanne et al., 2009). Additionally, Anderson and Olsen found that a higher BMI in stroke patients was associated with positive health indicators, such as non-smoking and nondrinking, suggesting that these positive lifestyles aspects may help to explain the paradoxical survival of obese stroke patients (Andersen and Olsen, 2013).

The link between severity of stroke, brain lesion and this “obesity paradox” is less clear, but some studies suggest that obese patients have less severe strokes and die less from neurological damage (Vemmos et al., 2011, Ryu et al., 2011).
When Vemmos and colleagues explored the different causes of death of 2785 patients with ischaemic and haemorrhagic first-ever strokes, the obese individuals had the lowest rate of mortality from neurological damage (3.2%) when compared with the overweight (7.5%) and normal weight (8.9%) groups ($p=0.0001$) (Vemmos et al., 2011). Surprisingly, the differences on rates of mortality from cardiovascular deaths were not statistically significant across BMI categories ($p=0.115$).
Ryu and his colleagues found that BMI was inversely associated with the NIHSS score in 1592 ischaemic strokes. Thus, patients with a low BMI had more severe strokes (and were more likely to have strokes due to cardioembolism) and patients with a high BMI had less severe strokes (and had more strokes due to small-vessel occlusion) (Ryu et al., 2011).
These findings could contribute to the explanation of the obesity paradox and explain the importance of the adjustment for stroke severity in studies exploring the association between BMI and mortality.

Primary versus secondary prevention of stroke – interpretation of the available data

While some authors do not accept the existence of an “obesity paradox”, claiming that it is simply an epidemiological association and supporting the view that the intervention for obesity will reduce the burden of stroke and it should start in the hyper-acute period after stroke (Kernan et al., 2013), other authors claim that not all patients classified as overweight or obese (grade 1), particularly those with chronic diseases, can be assumed to require weight loss treatment (Heymsfield and Cefalu, 2013), and no data are available to support recommendations to reduce body weight in (obese) patients after stroke (Scherbakov et al., 2011).

The results of the present study (chapter 4) suggest, once again, that a distinction needs to be made between the guidelines for primary and secondary prevention of stroke. It is well established that, in the healthy population, excess body fat increases the risk of mortality and the risk of stroke. This applies not only to BMI (Strazzullo et al., 2010, Wang et al., 2013, Calle et al., 1999, Berrington de Gonzalez et al., 2010) but also to several markers of abdominal obesity, such as WC (Winter et al., 2008, Suk et al., 2003, Bodenant et al., 2011, Jacobs et al., 2010, Pischon et al., 2008). However, when the outcomes are assessed in those who have had a stroke, being obese or having a larger WC is associated with a better survival and does not increase (or can even decrease) the risk of a recurrent stroke. In other words, being overweight or obese may impact patients with stroke differently than it does healthy subjects.

Strengths

The main merits of this study are the relatively large sample size, where one researcher (author) recruited all patients, collected all the baseline information and consistently analysed all the outcome data, that was available for the entire study population. Additionally, it captures any hospital admission that occurred anywhere in England, during the 6 month follow-up period. Many studies of the impact of malnutrition only looked at the outcomes of the first admission, not being able to report any outcome after the hospital discharge (Correia and Waitzberg, 2003, Raslan et al., 2010) and, to our knowledge, none of the published studies in the area of malnutrition were able to capture hospital readmissions at a national level. Lim et al admit that, because they were not able to monitor the study patients readmitted to other hospitals, an underestimation of the readmission rates may have occurred (Lim et al., 2012).

HES was the system chosen to capture hospital readmission and potential recurrent strokes. In a study that aimed to validate self-reported strokes in a longitudinal UK cohort, HES was the most efficient method of validation, when compared with manual extraction from hospital notes and corresponding with GPs (Britton et al., 2012). HES had the additional advantage of not requiring patient contact after discharge.

Moreover, the current study included patients without limitations of age (>18 years), gender or stroke severity, and did not exclude patients who lacked capacity to consent to participate or patients with severe communication problems, which is very common in the acute stage after stroke. In these cases, the researcher always tried to contact and meet with their next of kin (sometimes after working hours), who would be able to provide assent and information relevant for the study (e.g. usual weight and unintentional weight loss in the last months). This is particularly important to avoid a selection bias, which has been reported in national registries of strokes. For example, the Registry of the Canadian Stroke Network reported that the participation rate never exceeded half of the eligible patients (Tu et al., 2004), while the equivalent participation rates for the present study were 95% (or 91% if we include the patients who were not weighed due to the severity of their illness).

For the 21 patients who were not weighed within the first 3 days after stroke due to the severity of their illness, as they were not considered for any active treatment, the poor outcome of these patients is more likely to have been related to stroke severity (including cases of patients who were found at home, unresponsive, a few days after the stroke), and less likely to be associated with their nutritional status. Furthermore, the characteristics of the patients included in the study are in line with published figures (Carroll et al., 2001, RCP, 2012), such as the percentage of patients who had an ischaemic stroke (87 %) and the proportion of patients aged 65 and older (80%), This indicates that the study sample was representative of the stroke population in the U.K., suggesting minimal risk of selection bias.

Another positive and exclusive aspect of this study (when compared to all other studies exploring the association between BMI and mortality) is that it took into consideration indicators of a poor nutritional status, such as unintentional weight loss in the period preceding the baseline data collection (previous 3 to 6 months). Individuals who are normal weight, overweight or obese may also be at risk of malnutrition if, for example, the person presents a recent involuntary weight loss. BMI is an indicator of a chronic protein-energy status but recent unintentional weight loss reflects acute changes in nutritional status (Elia, 2000). In the present study, patients who lost weight before having a stroke were more likely to die and more likely to have a longer LOS and be more costly, independent of age, gender, ethnicity, type of stroke, severity of stroke and stroke risk factors, demonstrating the clinical importance of assessing unintentional weight loss before a stroke.

Limitations

The major limitations of this study were the lack of information regarding changes in body weight during follow-up and regarding the proportion of patients who were referred to a dietitian, as well as the type or length of any nutritional intervention they may have received (thus, dietetic intervention is an unmeasured confounder). In fact, this is an area that deserves further investigation. As mentioned in the "Methods" section (Baseline data collection - page 147), both tools were applied by the same person (the author) to avoid missing data as, in the vast majority of the cases, the NST was not fully completed by the staff (statement based on observation while collecting data). Thus, although I screened all the patients for my study (using 2 NST), it is very unlikely that all patients were screened by the nursing staff using the locally applied NST. Furthermore, of those who were screened by the nursing staff and considered at high risk of malnutrition, I do not how many were referred to a dietitian, and of those who were referred, I do not know how many received any intervention, neither the type nor the length of the nutritional intervention (with appropriate measures of prescription and compliance). In this study, these data would be extremely difficult to collect because of the current organisation of the stroke services in London, i.e., if I recruit a patient in the hyper-acute Stroke Unit of Princess Royal University Hospital (within 2 days post stroke) and he/she is then transferred to his local Stroke Unit (which may be Lewisham Hospital in London or a neuro-rehabilitation unit in Yorkshire) on the 3rd day post-stroke, I am not able to collect information regarding dietetic referral or potential intervention that the patient may have received in his/her local unit and after being discharged from hospital.

As discussed before, in "Chapter 1: Introduction / 1.1) Malnutrition / Potential benefits of nutritional intervention (page 25)", there are different types of nutritional interventions and these can result in a number of benefits, potentially changing the outcomes that I am measuring.

An ideal study would be conducted in a stroke unit that has no nutritional screening in place or any type of dietetic input to provide nutritional support, eliminating the effect that nutritional interventions can have on outcomes.

Nonetheless, it should be noted that even in places where nutritional screening exists and dietetic input is available, the system fails to adequately recognise and treat malnutrition. In 2007, Lamb and his colleagues conducted a cross-sectional study in adults under the specialities of general medicine, general surgery, orthopaedics and critical care of an acute hospital in North-East England, to measure the compliance with policy on screening for malnutrition (by ward staff) and further dietetic referral. In a single day, 328 inpatients met the inclusion criteria, of which only 226 (69%) had the local NST applied. Of these, 31 (14%) were identified as being at high risk of malnutrition, and of these, only 14 (45%) were appropriately referred for dietetic advice. Furthermore, when the researchers assessed the remaining 102 unscreened patients, they found that 14 (14%) patients were also at high risk of malnutrition, i.e. these patients were unrecognised by ward staff and should also have been referred for dietetic intervention (Lamb et al., 2009). Other authors have highlighted the significant proportion of malnourished patients that often go unrecognised and, therefore, untreated (McWhirter and Pennington, 1994, Lim et al., 2012) and it is likely that the same problem will apply to this study.

Another limitation is related to the patients who had a stroke and died before hospital arrival were not included in the analysis. This is a difficult limitation to overcome, and was present in the majority of the studies that explored the association between BMI and mortality post-stroke (Vemmos et al., 2011, Doehner et al., 2013, Olsen et al., 2008). Similarly, HES does not capture strokes that did not result in hospitalisation or that did not occur in England.

This study had the advantage of including a parameter that is rarely measured, the WC, which is considered the best surrogate method of visceral adiposity across a wide age range (Onat et al., 2004). In a few patients with larger WC, the difference between WC of individuals standing up and lying down was greater than 2 cm. This is a potential limitation of the methods used to determine WC in bedbound patients. However, the alternative of excluding patients who were bedbound would probably create a strong selection bias. Hence, the risk of having a minor error associated with the measurements of WC in all recruited patients seems to be more acceptable than the risk of excluding a significant part of recruited patients due to their inability to (safely) stand up.

Furthermore, it would be interesting to analyse functional outcomes, such as the degree of disability or dependence for activities of daily living in relation to BMI. The present study was not designed to capture this information, i.e. it was agreed that patients would not be contacted post recruitment in order to maximise the number of patients recruited. In a future study, short-term and long-term indicators of poor functional outcome measured by, for example, the modified Rankin Scale and the Barthel Index (Sulter et al., 1999), would help to address this question. Dohener and his colleagues analysed the association between body mass index and a combined endpoint of mortality and severe functional disability (as defined by modified Rankin scale > 3 or Barthel Index < 60) in 1374 patients at 30 months post-stroke or TIA (Doehner et al., 2013). They found that, after adjusting for potential confounders, obese (and overweight) patients had a significantly lower risk of this combined endpoint, when compared to the normal weight (reference) group. However, this study presents several limitations, such as, being a subanalysis of an intervention study, BMI data was available for only 34% of study participants, inclusion of TIAs and lack of separated multivariable analysis for functional disability. Thus, future studies are needed to address this question adequately.

In the present study, causes of death were not investigated because:

- the source of information to obtain mortality data, i.e. Summary Care Records, provides the date of death (when applicable) but not cause of death
- even if cause of death was available, the relatively small sample size of this study would not allow for a stratified analysis by cause of death (the same problem was raised and discussed for ethnicity, in section "results" of chapter 3, where the sample size is slightly bigger). However, as stated before in the discussion of chapter 3, a South Korean study with 34132 acute ischaemic strokes conducted a stratified analysis by cause of death (divided by "cancer", "vascular" and "other"), and found that the inverse association between BMI and mortality remains preserved in the multivariable cause-specific analyses (Kim et al., 2012). This study suggests that the association between BMI and mortality is independent of cause of death (as well as age). Another study explored the different causes of death (neurological damage, infection, cardiovascular, recurrent stroke, malignancy and other causes) in different BMI groups of 2785 patients with ischaemic and haemorrhagic first-ever strokes. Cause-specific rates of mortality were not significantly different across BMI categories, except for 2 causes of death (recurrent strokes and neurological damage, p=0.0001 and p=0.037 respectively) where the lower death rates were attributed to the obese group (Vemmos et al., 2011).

Finally, the 6-month follow-up time of this study was relatively short (due to time constraints imposed by the PhD programme), and it would be interesting to see whether the long-term outcomes remain similar. Other authors have reported that survival rates at 1 week, 1 month and 10 years post-stroke remain significantly lower over time for overweight and obese (first ever stroke) patients, when compared with the normal weight group (Vemmos et al., 2011), but we do not know whether this applies to all the outcome measured in the present study, in a multiethnic population of first and recurrent strokes.

A checklist used to report standards for observational studies (STROBE, i.e. STrengthening the Reporting of OBservational studies in Epidemiology (von Elm et al., 2008)) was applied to this study and can be found in appendix 4.21.

4.6 - Conclusion

Patients at high risk of malnutrition (as identified by MUST or GSTT NST) have a significantly increased risk of mortality, a longer LOS and a greater cost of hospitalisation, at 6 months post stroke.

Whether nutritional interventions provided in hospital are sufficient to improve outcomes in these patients remains to be clarified, as well as the best timing and type of feeding routes.

The author of this thesis collaborated in the process to develop the 4th edition of the “National clinical guidelines for stroke” (RCP, 2012), created by the Royal College of Physicians Intercollegiate Stroke Working Party, where key aspects of the nutritional support of stroke patients at risk of malnutrition were systematically reviewed with the aim of providing evidence-based guidelines for use in clinical practice (Gomes et al., 2014).

As part of this work, a systematic review entitled “Oral nutritional supplements in patients at risk of malnutrition who have had a stroke” was undertaken. Searches were conducted through to 31st October 2011 using five electronic databases (Embase, Medline, Cinahl, Cochrane Library and Web of Science), and 1084 abstracts were retrieved of which no studies met all the inclusion criteria. It was concluded that, to that date, there was a lack of good quality evidence supporting the role of ONS in the management of patients who are malnourished or at risk of malnutrition following acute stroke. These results were presented as an oral communication at the 21st European Stroke Conference (appendix G).

The limited data available suggest the need for adequately powered randomised controlled trials, using validated screening procedures, to investigate the effects of oral nutritional supplements on clinical, nutritional and cost outcomes.

Further research is also needed on the most effective types and duration of nutritional support. Given that malnutrition may take a considerable amount of time (e.g. several months) to develop, studies that examine the effect of short term nutritional interventions (sometimes confined to hospital admission) are not allowing enough time to treat any pre-existing nutritional deficiencies or to make a difference on outcomes.

Alongside hospital-based interventions for those patients who are admitted already malnourished, early or preventative nutritional interventions in the community (i.e., strategies to improve nutritional status of the population at risk for stroke) may be needed, either for people living at home or institutionalised. For instance, some authors suggest that the combination of physical exercise and nutritional supplementation should be considered, due to its potential to counteract muscle weakness (i.e. increase muscle power and functional gains) in frail elderly individuals (Bonnefoy et al., 2003).

As mentioned previously, guidelines on secondary prevention of stroke recommend patients who are overweight or obese should be advised to lose weight (RCP, 2012, AHA, 2009).

The results of the present study showed that being obese and having a larger WC was associated with reduced mortality and does not increase the risk of a recurrent stroke. This, in conjunction with a growing body of evidence that supports “the obesity paradox” after stroke (as demonstrated in section 3.1), may emphasise the need to amend the current guidelines. However these are observational studies, which identify associations, not causality. Future research could include randomised controlled trials of interventions for weight reduction on secondary prevention of stroke.

Chapter 5

Final conclusion

Summary of achievements and findings of this thesis

In the first study (chapter 2), the predictive validity of the GSTT NST was tested in hospitalised elderly care and stroke patients.

Results demonstrated that patients at high risk of malnutrition had a significantly increased rate of mortality (at 1 month, 3 months, 6 months and 1 year) and a tendency for a longer LOS, when compared to patients at medium and low risk. This suggested that the NST can be used to predict negative outcomes in the elderly and stroke hospitalised population, although more research was needed to make definitive conclusions, given the small number of stroke patients included in this sample (n=25). Therefore, an adequately powered study was designed to investigate the predictive validity of this tool and another recommended tool (MUST) in patients who have had a stroke (chapter 4).

Given the emerging evidence of a paradoxical survival in obese stroke patients, a literature review was conducted to capture and compare all the published studies that explored the association between BMI and mortality in patients who suffered a stroke.

Several studies were identified with ischaemic and haemorrhagic strokes, with different groups of age, with first and recurrent strokes, in various countries with different cut-offs to define BMI groups. All of them had limitations and further investigation was needed, especially in multi-ethnic populations, such as the population of London.

An ongoing population-based register (which covers a multiethnic population of 234 533 inhabitants and records strokes that occurred in South London), was used as the source of data for the second study (chapter 3), to determine the association between BMI and mortality after a first-ever stroke.

After adjusting for possible confounders and having the normal weight category as reference group, the risk of mortality (up to 8 years) was higher for the underweight and lower for the overweight category. BMI was an independent significant risk factor for mortality in a multiethnic population of individuals who had a stroke for the first time.

This "obesity paradox" needed to be scrutinised and justified the evaluation of other relevant outcomes, such as the risk of having a recurrent stroke, as well as other indicators of nutritional status and distribution of body fat. The third study was, therefore, designed to investigate this (chapter 4).

The relationship between BMI, WC, risk of malnutrition and outcomes at 6 months post stroke was prospectively analysed. 550 patients were recruited and assessed within 72h of admission to two London-based hospitals.
Results showed that patients at high risk of malnutrition (as identified by MUST or GSTT) had a significantly increased risk of mortality, a longer LOS and a greater cost of hospitalisation, at 6 months post stroke, independent of age, gender, ethnicity, type of stroke, severity of stroke and stroke risk factors. The results also showed that the higher the BMI and the WC quartile, the lower the rate of mortality, and there were no significant associations between BMI or WC and stroke recurrence.
Further research is needed to determine whether nutritional support (including type and duration) improves the poor outcomes of those patients identified as at high risk of malnutrition.

A systematic review entitled "ONS in patients at risk of malnutrition who have had a stroke" was also conducted (as part of a review of national clinical guidelines on stroke care) and it was concluded that there is a lack of good quality evidence supporting the role of ONS in the management of patients at risk of malnutrition following acute stroke.

Original aspects of this thesis

In Chapter 3, I was able to identify, summarise and analyse all the existing published studies that have explored the association between BMI and mortality post stroke. After showing the clinical heterogeneity and the limitations of these studies (included the lack of studies conducted in a multiethnic population), my prospective study was the first to demonstrate that BMI is a statistically significant independent risk factor for mortality in a multiethnic population of individuals who had a first stroke. These results account for the correct distinction between underweight and normal weight patients and apply to both early (6 months) and late (up to 8 years) follow-up times, as well as to total and ischaemic strokes and to patients aged under 65 years or 65 and over, and included the adjustment for the effect of ethnicity. This is another important piece of information that can be added to the growing body of evidence that supports the "obesity paradox" post stroke.

Chapter 4 described a study that, for the first time, was able to:

- validate a nutrition screening tool for stroke patients, which was an area identified as lacking a strong evidence base
- show that risk of malnutrition, assessed by these tools, is a statistically significant predictor of mortality, LOS and hospitalisation costs at 6 months post-stroke, independently of age, gender, ethnicity, type of stroke, severity of stroke and stroke risk factors
- determine the proportion of patients who presented unintentional weight loss prior to stroke and demonstrate that the isolated effect of this unintentional weight loss (an indicator of risk of malnutrition) is also a statistically significant predictor of mortality, LOS and hospitalisation costs at 6 months post-stroke

The methodology used to determine LOS and hospitalisation costs is unique in this study as it captures national data, i.e., any hospital admission that occurred anywhere in England, during the 6 month follow-up period. Other studies have determined these outcomes based simply on the first admission or on readmissions that occurred to the same hospital

- use several markers of nutritional status (BMI, WC, risk of malnutrition, unintentional weight loss prior to stroke) for every recruited patient, measured by a single researcher, and also a variety of outcomes (mortality, stroke recurrence, LOS, hospitalisation costs and hospital readmissions). Many authors that explored the association between BMI and mortality admitted that the main limitation of their studies is the lack of measures of distribution of body fat or other indicators of nutritional status.

Several studies conducted in the stroke population have explored the association between BMI and mortality, and a few have looked at the relationship between BMI and stroke recurrence, but no published studies have assessed the effect of abdominal obesity (e.g. measured by WC) on mortality or stroke recurrence. The current study explored all these associations, and did it with a methodology that is notably superior to the ones reported by all the other studies. I would like to highlight that, as opposed to other published studies, in the present study a single researcher was responsible for all recruitment (and managed to recruit 95% of all eligible patients), collected all the baseline information and consistently analysed all the outcome data that was available for the entire study population.

Thus, this high quality study was the first to show the results on a combination of exposures and outcomes in a multiethnic population with first and recurrent, ischaemic and haemorrhagic strokes. It showed that, the higher the BMI (divided by 4 categories, with an adequate distinction between underweight and normal weight) and the WC quartile, the lower the rate of mortality (although WC was not a significant predictor of mortality in the multivariable analysis), and there were no significant associations between BMI or WC and stroke recurrence. Equally, overweight and obese patients were not more likely to have a longer LOS, or to cost more or to have more hospital readmissions. All these results also reinforce the idea of the “obesity paradox” after stroke, and show that WC does not add any predictive value for stroke outcomes (as opposed to what is suggested by primary prevention studies).

The data from my studies will be important to inform the design of future RCT. For example, now that we know how to identify those who are at high risk of malnutrition (using a validated screening tool for the stroke population) and are more likely to have poor outcomes (mortality, LOS, costs), the next step is to investigate whether we can change these outcomes by providing adequate nutritional support.

As mentioned before, there is lack of good quality evidence supporting the role of nutritional interventions (e.g. ONS) in the management of acute stroke patients that are malnourished or at risk of malnutrition, and the reason for the lack of beneficial effects of some of these interventions may be related with the incorrect identification (i.e. use of non validated tools) of those who are more likely to benefit from them.

Contributions and final remarks

The health system has the responsibility of giving accurate advice and information to patients, and helping healthcare professionals to deliver targeted interventions. In addition, there is a continuous need to evaluate healthcare practices using evidence-based methods.

Firstly, this thesis contributed to the evaluation of nutrition screening practices and the results reinforced the importance of screening stroke patients.

In fact, a recent cohort study (with more than 36000 ischaemic stroke patients) that explored the association between process of care received and 30-day mortality in England, highlights the importance of nutrition screening and adequate nutrition after acute stroke (Bray et al., 2013). Among several bundles of care, authors identified two bundles that were associated with reduced mortality: nutrition screening and formal swallow assessment within 72 hours where appropriate, and antiplatelet therapy where appropriate and adequate fluid and nutrition for the first 72 hours.

In 2003, an audit evaluated the outcomes of 2 groups of acute stroke patients (n=200 patients each): one group admitted before implementation of guidelines for nutrition support and the other group admitted after implementation. These guidelines included recommendations for screening for nutritional risk, dysphagia and other impairments that affect eating. Several significant improvements were observed, including lower rates of chest infection, aspiration pneumonia and/or sepsis in the post-implementation group, and a significant reduction in the number of patients for whom nutritional support decision making was deferred beyond 5 days of admission (Perry and McLaren, 2003).

Further studies are needed to evaluate the individual process measures (in particular the individual effects of screening and nutritional support) in more detail, as in both studies changes cannot be attributed to individual components.

Secondly, this thesis also contributed to the evaluation of practices imposing “ideal” BMI ranges in stroke patients and the potential need to shift emphasis from BMI to WC.

The idea of the “obesity paradox” in a stroke population may not be easily accepted by some members of the scientific community, although this is not the first or only paradoxical association to be reported. It should be noted that, besides the growing body of evidence supporting the “obesity paradox” - not only in stroke and wasting diseases but also in cardiovascular diseases, such as coronary artery disease (Uretsky et al., 2007) or diabetes type II (Doehner et al., 2012) - other paradoxical associations have also been reported in the stroke population. For example, some studies found a better prognosis (including mortality) in ischaemic stroke patients who had higher serum cholesterol levels after the event (Vauthey et al., 2000, Zuliani et al., 2004).

As suggested before, it is possible that a distinction needs to be made between the guidelines for primary and secondary prevention of stroke.

Future research recommendations

The better outcomes of patients who are overweight and obese or have a larger WC suggest that current guidelines on weight management of these patients may need to be amended, however future randomised controlled trials of interventions for weight reduction (or diet modification) on secondary prevention of stroke are needed.

These randomised controlled trials would need to be well designed and adequately powered to determine the effect of weight reduction on several outcomes of overweight and obese patients who have suffered a stroke.

In an ideal study, overweight and obese acute stroke patients would be allocated either to the control group (which would aim to maintain weight but would receive advice to improve the nutritional profile of their diet) or to the intervention group (which would also receive advice to improve the nutritional profile of the diet but would aim for weight reduction, which would be planned, balanced and supervised by an experienced qualified professional). The duration of the trial (intervention and follow-up) would need to be at least 1 year, and during this period, both groups would have monthly contact with the people delivering the intervention (via clinics or telephone) to reinforce compliance to the diet and to encourage the participant to achieve or maintain the nutritional targets.

The treatment received to control other risk factors (e.g. anticoagulation and antiplatelet therapy, smoking cessation plans, etc.) should be similar in both groups.

Primary outcomes would be mortality, functional outcomes and recurrent stroke; secondary outcomes would be nutritional outcomes and quality of life.

Ideally, the intervention group would allow for a combination of strategies that would better fit the participant, who would receive an individualised plan designed to sustain a long-term weight loss (blinding to patients and people administering treatment would not be possible). The control group would aim to follow a diet with no caloric restriction but with an improved nutritional profile, such as salt reduction, replacement of saturated fat with mono and unsaturated fats, decrease of animal protein and increase of plant protein from pulses and nuts. This comparison has the advantage of distinguishing the effect of weight reduction per se from the effect of dietary modification (with no weight loss) on outcomes, but it is a complex project that would require feasibility testing and pilot work.

The definition of the inclusion criteria would also be a crucial step in this trial. One would argue that it would be ideal to include patients fed via nasogastric tubes, since it is easy to control the caloric (and nutrient) intake for these patients and we should be able to extrapolate the results to the entire overweight and obese stroke population. However, when the nasogastric tube is removed, it is possible (and often observed) that an unintentional weight loss may occur (particularly if the patient requires texture modification of the diet). Thus, it would better to include only overweight and obese patients who have an intact swallowing function and can follow a normal diet. The intervention could start immediately after stroke for those who meet the inclusion criteria (including no swallowing difficulties). For those with dysphagia, recruitment and the beginning of intervention could be delayed for 2 weeks after stroke (when a swallowing improvement is expected for the majority of patients with potential for recovery).

Another difficulty includes the possible occurrence of a significant weight reduction in the control group. Thus, participants in the control group should also be weighed by the end of the trial to allow for a comparison with the weight reduction obtained in the intervention group.

Compliance and attrition rates are a common problem in long-term dietary intervention trials. Therefore the number of patients recruited should be higher than necessary to account for this issue and financial compensation should be considered to maximise compliance.

A further recommendation to improve the quality of future research is related with the assessment of height, weight and BMI in stroke trials and registers.

The proportion of patients whose BMI is not assessed, even when weight and height were explicitly stated to be routinely collected, varies from approximately 50% in national stroke registers (SRP, 2001-2003, Olsen et al., 2008) to 66% (Doehner et al., 2013) or 80% (Dennis et al., 2006) in clinical trials. Given the emerging impact of BMI on post-stroke outcomes and the need to avoid selection bias, regular assessment of these measurements in stroke trials and registers, as well as in clinical settings should be recommended.

In the SLSR, it would be important to amend the protocol of data collection regarding weight and BMI. The following recommendations are made:

- SLSR researchers/fieldworkers should have an active role in collecting weight and height measurements from patients able to stand up, after receiving appropriate training
- SLSR researchers/fieldworkers should be able to use simple and quick alternative measurements to estimate height, such as, ulna length. “Method used to measure height” should be another variable added to the data collection sheet

- wall fixed stadiometers should be made available in every ward/room where the SLSR data is collected
- it would be the responsibility of the nursing staff to weigh bedbound patients, therefore nurse coordinators should emphasise the need to weigh any patient within 72h (and assure that regular audits are conducted to measure compliance).

While there is a growing interest of researchers and clinicians in exploring the associations between BMI and mortality or stroke recurrence, due to the "obesity paradox" effect, little is known about the functional outcomes of overweight and obese patients (Doehner et al., 2013).

Additionally, there is a paucity of data on health outcomes from the patient's perspective, such as quality of life and patient satisfaction and the association between malnutrition and quality of life after a stroke has not yet been explored.

Quality of life can be profoundly affected by a stroke (Muren et al., 2008) and it was suggested that malnutrition, through different ways, could lead to an impairment of quality of life in elderly patients (Jones, 2006); however, the association between this condition and quality of life after a stroke is not known and deserves to be explored.

Reference List

AGE UK. 2013. *Later Life in the United Kingdom* [Online]. Available: http://www.ageuk.org.uk/Documents/EN-GB/Factsheets/Later_Life_UK_factsheet.pdf?dtrk=true [Accessed 21 October 2013].

AHA 2009. Comprehensive Overview of Nursing and Interdisciplinary Care of the Acute Ischemic Stroke Patient: A Scientific Statement From the American Heart Association. American Heart Association/American Stroke Association (available in http://stroke.ahajournals.org/content/40/8/2911.full.pdf).

AMARAL, T. F., MATOS, L. C., TAVARES, M. M., SUBTIL, A., MARTINS, R., NAZARE, M. & SOUSA, P. N. 2007. The economic impact of disease-related malnutrition at hospital admission. *Clinical Nutrition,* 26**,** 778-784.

ANDERSEN, K. K. & OLSEN, T. S. 2013. The obesity paradox in stroke: Lower mortality and lower risk of readmission for recurrent stroke in obese stroke patients. *International Journal of Stroke***,** [Preprint].

ANDERSEN, K. K., OLSEN, T. S., DEHLENDORFF, C. & KAMMERSGAARD, L. P. 2009. Hemorrhagic and Ischemic Strokes Compared: Stroke Severity, Mortality, and Risk Factors. *Stroke,* 40**,** 2068-2072.

ANTHONY, P. S. 2008. Nutrition screening tools for hospitalized patients. *Nutrition in Clinical Practice,* 23**,** 373-382.

AQUILANI, R., LA ROVERE, M. T., FEBO, O., BOSCHI, F., IADAROLA, P., CORBELLINI, D., VIGLIO, S., BONGIORNO, A. I., PASTORIS, O. & VERRI, M. 2012. Preserved muscle protein metabolism in obese patients with chronic heart failure. *International Journal of Cardiology,* 160**,** 102-108.

AXELSSON, K., ASPLUND, K., NORBERG, A. & ALAFUZOFF, I. 1988. Nutritional status in patients with acute stroke. *Acta Med Scand,* 224**,** 217-24.

BALDWIN, C., SPIRO, A., AHERN, R. & EMERY, P. W. 2012. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. *Journal of the National Cancer Institute,* 104**,** 371-85.

BAUER, J. M., KAISER, M. J. & SIEBER, C. C. 2010. Evaluation of nutritional status in older persons: nutritional screening and assessment. *Current Opinion in Clinical Nutrition and Metabolic Care,* 13**,** 8-13.

BERRINGTON DE GONZALEZ, A., HARTGE, P., CERHAN, J. R., FLINT, A. J., HANNAN, L., MACINNIS, R. J., MOORE, S. C., TOBIAS, G. S., ANTON-CULVER, H., FREEMAN, L. B., BEESON, W. L., CLIPP, S. L., ENGLISH, D. R., FOLSOM, A. R., FREEDMAN, D. M., GILES, G., HAKANSSON, N., HENDERSON, K. D., HOFFMAN-BOLTON, J., HOPPIN, J. A., KOENIG, K. L., LEE, I.-M., LINET, M. S., PARK, Y., POCOBELLI, G., SCHATZKIN, A., SESSO, H. D., WEIDERPASS, E., WILLCOX, B. J., WOLK, A., ZELENIUCH-JACQUOTTE, A., WILLETT, W. C. & THUN, M. J. 2010. Body-Mass Index and Mortality among 1.46 Million White Adults. *New England Journal of Medicine,* 363**,** 2211-2219.

BHATNAGAR, P., SCARBOROUGH, P., SMEETON, N. & ALLENDER, S. 2010. The incidence of all stroke and stroke subtype in the United Kingdom, 1985 to 2008: a systematic review. *BMC Public Health,* 10**,** 539.

BISTRIAN, B. R., BLACKBURN, G. L., VITALE, J., COCHRAN, D. & NAYLOR, J. 1976. Prevalence of malnutrition in general medical patients. *JAMA,* 235**,** 1567-1570.

BODEN-ALBALA, B., ELKIND, M. S., WHITE, H., SZUMSKI, A., PAIK, M. C. & SACCO, R. L. 2009. Dietary total fat intake and ischemic stroke risk: the Northern Manhattan Study. *Neuroepidemiology,* 32**,** 296-301.

BODENANT, M., KUULASMAA, K., WAGNER, A., KEE, F., PALMIERI, L., FERRARIO, M. M., MONTAYE, M., AMOUYEL, P., DALLONGEVILLE, J. & PROJECT, M. 2011. Measures of Abdominal Adiposity and the Risk of Stroke The MOnica Risk, Genetics, Archiving and Monograph (MORGAM) Study. *Stroke,* 42**,** 2872-U301.

BONNEFOY, M., CORNU, C., NORMAND, S., BOUTITIE, F., BUGNARD, F., RAHMANI, A., LACOUR, J. R. & LAVILLE, M. 2003. The effects of exercise and protein–energy supplements on body composition and muscle function in frail elderly individuals: a long-term controlled randomised study. *British Journal of Nutrition,* 89**,** 731-738.

BOUILLANNE, O., DUPONT-BELMONT, C., HAY, P., HAMON-VILCOT, B., CYNOBER, L. & AUSSEL, C. 2009. Fat mass protects hospitalized elderly persons against morbidity and mortality. *American Journal of Clinical Nutrition,* 90**,** 505-510.

BRAY, B. D., AYIS, S., CAMPBELL, J., HOFFMAN, A., ROUGHTON, M., TYRRELL, P. J., WOLFE, C. D. A. & RUDD, A. G. 2013. Associations between the organisation of stroke services, process of care, and mortality in England: prospective cohort study. *British Medical Journal,* 346.

BRITTON, A., MILNE, B., BUTLER, T., SANCHEZ-GALVEZ, A., SHIPLEY, M., RUDD, A., WOLFE, C. D. A., BHALLA, A. & BRUNNER, E. J. 2012. Validating self-reported strokes in a longitudinal UK cohort study (Whitehall II): Extracting information from hospital medical records versus the Hospital Episode Statistics database. *Bmc Medical Research Methodology,* 12.

BROTHERTON, A., SIMMONDS, N. & STROUD, M. 2010. Malnutrition Matters - Meeting Quality Standards in Nutritional Care: A Toolkit for Commissioners and Providers in England. Redditch: BAPEN.

BROWNIE, S. 2006. Why are elderly individuals at risk of nutritional deficiency? *Int J Nurs Pract,* 12**,** 110-118.

BRUEGGENJUERGEN, B., ROSSNAGEL, K., ROLL, S., ANDERSSON, F. L., SELIM, D., MUELLER-NORDHORN, J., NOLTE, C. H., JUNGEHUELSING, G. J., VILLRINGER, A. & WILLICH, S. N. 2007. The impact of atrial fibrillation on the cost of stroke: The Berlin acute stroke study. *Value in Health,* 10**,** 137-143.

CAIRELLA, G., SCALFI, L., BERNI, C. R., GARBAGNATI, F., GENTILE, M. G., GIANNI, C., MARCELLI, M., MOLFINO, A., MUSCARITOLI, M., PAOLUCCI, S., PRATESI, L., ROSSI, F. F., SCOGNAMIGLIO, U., TARI, Y., TROIANO, E. & BRANCA, F. 2004. Nutritional management of stroke patients. *Rivista Italiana di Nutrizione Parenterale ed Enterale,* 22**,** 205-226.

CALLE, E. E., THUN, M. J., PETRELLI, J. M., RODRIGUEZ, C. & HEATH, C. W. 1999. Body-mass index and mortality in a prospective cohort of US adults. *New England Journal of Medicine,* 341**,** 1097-1105.

CAMPOS, A. C. L. & MEGUID, M. M. 1992. A critical appraisal of the usefulness of perioperative nutritional support. *American Journal of Clinical Nutrition,* 55**,** 117-130.

CARNETHON, M. R., DE CHAVEZ, P. J. D., BIGGS, M. L., LEWIS, C. E., PANKOW, J. S., BERTONI, A. G., GOLDEN, S. H., LIU, K., MUKAMAL, K. J., CAMPBELL-JENKINS, B. & DYER, A. R. 2012. ASsociation of weight status with mortality in adults with incident diabetes. *JAMA,* 308**,** 581-590.

CARROLL, K., ELIAHOO, J., MAJEED, M. & MURAD, S. 2001. Stroke incidence and risk factors in a population-based prospective cohort study. *Health Statistics Quarterly***,** 18-26.
CHANDRA, R. K. 1979. Nutritional deficiency and susceptibility to infection. *Bull World Health Organ,* 57**,** 167-77.
CHARNEY, P. 2008. Nutrition screening vs nutrition assessment: how do they differ?. *Nutrition in Clinical Practice,* 23**,** 366-372.
CHIMA, C. S., BARCO, K., DEWITT, M. L. A., MAEDA, M., TERAN, J. C. & MULLEN, K. D. 1997. Relationship of Nutritional Status to Length of Stay, Hospital Costs, and Discharge Status of Patients Hospitalized in the Medicine Service. *Journal of the American Dietetic Association,* 97**,** 975-978.
CHOI-KWON, S., YANG, Y. H., KIM, E. K., JEON, M. Y. & KIM, J. S. 1998. Nutritional status in acute stroke: undernutrition versus overnutrition in different stroke subtypes. *Acta Neurol Scand,* 98**,** 187-92.
CORREA LEITE, M. L., NICOLOSI, A., CRISTINA, S., HAUSER, W. A. & NAPPI, G. 2001. Nutrition and cognitive deficit in the elderly: A population study. *European Journal of Clinical Nutrition,* 55**,** 1053-1058.
CORREIA, M. I. T. D. & WAITZBERG, D. L. 2003. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. *Clinical Nutrition,* 22**,** 235-239.
CRARY, M. A., CARNABY-MANN, G. D., MILLER, L., ANTONIOS, N. & SILLIMAN, S. 2006. Dysphagia and nutritional status at the time of hospital admission for ischemic stroke. *Journal of Stroke and Cerebrovascular Diseases,* 15**,** 164-71.
CRICHTON, S. L., WOLFE, C. D. A., RUDD, A. G. & MCKEVITT, C. 2012. Comparison of provision of stroke care in younger and older patients: findings from the South london stroke register. *Stroke research and treatment,* 2012**,** 319581.
CRISTENSEN, L., KRIEGER, D. & CRISTENSEN, H. 2010. Risk factors for stroke are different in the very old. *International Journal of Stroke.* Blackwell Publishing Ltd.
CURIONI, C., ANDRE, C. & VERAS, R. 2009. Weight reduction for primary prevention of stroke in adults with overweight or obesity (review). *Cochrane Database of Systematic Reviews***,** Art. No.: CD006062.
DAVALOS, A., RICART, W., GONZALEZHUIX, F., SOLER, S., MARRUGAT, J., MOLINS, A., SUNER, R. & GENIS, D. 1996. Effect of malnutrition after acute stroke on clinical outcome. *Stroke,* 27**,** 1028-1032.
DAVIS, J. P., WONG, A. A., SCHLUTER, P. J., HENDERSON, R. D., O'SULLIVAN, J. D. & READ, S. J. 2004. Impact of premorbid undernutrition on outcome in stroke patients. *Stroke,* 35**,** 1930-1934.
DENNIS, M. 2003. Poor nutritional status on admission predicts poor outcomes after stroke - Observational data from the FOOD trial. *Stroke,* 34**,** 1450-1455.
DENNIS, M., LEWIS, S., CRANSWICK, G. & FORBES, J. 2006. FOOD: A multicentre randomized trial evaluating feeding policies in patients admitted to hospital with a recent stroke. *Health Technology Assessment,* 10**,** 1-91.
DEPARTMENT OF HEALTH 2012. Payment by Results tariff information spreadsheet for 2012 to 2013. England: Department of Health.
DESPRES, J. P. & LEMIEUX, I. 2006. Abdominal obesity and metabolic syndrome. *Nature,* 444**,** 881-887.
DETSKY, A., MCLAUGHLIN, BAKER, J., JOHNSTON, N., WHITTAKER, S., MENDELSON, R. & JEEJEEBHOY, K. 1987. What is subjective global

assessment of nutritional status? *Journal of Parenteral and Enteral Nutrition,* 11**,** 8-13.
DOEHNER, W., ERDMANN, E., CAIRNS, R., CLARK, A. L., DORMANDY, J. A., FERRANNINI, E. & ANKER, S. D. 2012. Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: An analysis of the PROactive study population. *International Journal of Cardiology,* 162**,** 20-26.
DOEHNER, W., SCHENKEL, J., ANKER, S. D., SPRINGER, J. & AUDEBERT, H. J. 2013. Overweight and obesity are associated with improved survival, functional outcome, and stroke recurrence after acute stroke or transient ischaemic attack: observations from the TEMPiS trial. *European Heart Journal,* 34**,** 268-277.
DONINI, L. M., SAVINA, C., ROSANO, A. & CANNELLA, C. 2007. Systematic review of nutritional status evaluation and screening tools in the elderly. *Journal of Nutrition Health & Aging,* 11**,** 421-432.
ELIA, M. 2000. Guidelines for Detection and Management of Malnutrition. Maidenhead (UK): Malnutrition Advisory Group of the British Association for Parenteral and Enteral Nutrition
ELIA, M. 2003. The "MUST" report. Nutritional screening of adults: a multidisciplinary responsibility. BAPEN.
ELIA, M. 2006. Nutrition and health economics. *Nutrition,* 22**,** 576-578.
ELIA, M., RUSSELL, C., STRATTON, R., TODOROVIC, V., EVANS, L. & FARRER, K. 2003. The ‘MUST’ explanatory booklet - a guide to the ‘Malnutrition Universal Screening Tool’ (‘MUST’) for Adults. BAPEN.
ELIA, M. & RUSSELL, C. A. 2009. Combating malnutrition; Recommendations for Action. A report from the Advisory Group on Malnutrition. Redditch: BAPEN.
ERDFELDER, E., FAUL, F. & BUCHNER, A. 1996. GPOWER: A general power analysis program. *Behavior Research Methods, Instruments, & Computers,* 28**,** 1-11.
FINESTONE, H. M., GREENE-FINESTONE, L. S., WILSON, E. S. & TEASELL, R. W. 1995. Malnutrition in stroke patients on the rehabilitation service and at follow-up: prevalence and predictors. *Arch Phys Med Rehabil,* 76**,** 310-6.
FLIER, J. S. 2004. Obesity wars: Molecular progress confronts an expanding epidemic. *Cell,* 116**,** 337-350.
FOLEY, N., FINESTONE, H., WOODBURY, M. G., TEASELL, R. & GREENE-FINESTONE, L. 2006. Energy and protein intakes of acute stroke patients. *Journal of Nutrition, Health and Aging,* 10**,** 171-175.
FOLEY, N., TEASELL, R., BHOGAL, S. & SPEECHLEY, M. 2012. Nutritional Interventions Following Stroke. Ontario: Evidence-Based Review of Stroke Rehabilitation.
FOLEY, N. C., MARTIN, R. E., SALTER, K. L. & TEASELL, R. W. 2009a. A Review of the Relationship Between Dysphagia and Malnutrition Following Stroke. *Journal of Rehabilitation Medicine,* 41**,** 707-713.
FOLEY, N. C., SALTER, K. L., ROBERTSON, J., TEASELL, R. W. & WOODBURY, M. G. 2009b. Which Reported Estimate of the Prevalence of Malnutrition After Stroke Is Valid? *Stroke,* 40**,** E66-E74.
FUNK, K. L. & AYTON, C. M. 1995. Improving Malnutrition Documentation Enhances Reimbursement. *Journal of the American Dietetic Association,* 95**,** 468-475.
FURIE, K. L., KASNER, S. E., ADAMS, R. J., ALBERS, G. W., BUSH, R. L., FAGAN, S. C., HALPERIN, J. L., JOHNSTON, S. C., KATZAN, I., KERNAN, W. N., MITCHELL, P. H., OVBIAGELE, B., PALESCH, Y. Y., SACCO, R. L.,

SCHWAMM, L. H., WASSERTHEIL-SMOLLER, S., TURAN, T. N., WENTWORTH, D., ON BEHALF OF THE AMERICAN HEART ASSOCIATION STROKE COUNCIL, C. O. C. N. C. O. C. C., INTERDISCIPLINARY COUNCIL ON QUALITY OF, C. & OUTCOMES, R. 2010. Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack. A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke***,** STR.0b013e3181f7d043.

GABAY, C. & KUSHNER, I. 1999. Acute-phase proteins and other systemic responses to inflammation. *New England Journal of Medicine,* 340**,** 448-54.

GALLAGHER-ALLRED, C. R., VOSS, A. C., FINN, S. C. & MCCAMISH, M. A. 1996. Malnutrition and clinical outcomes: the case for medical nutrition therapy. *J Am Diet Assoc,* 96**,** 361-6, 369.

GARDENER, H., RUNDEK, T., WRIGHT, C. B., ELKIND, M. S. V. & SACCO, R. L. 2012. Dietary Sodium and Risk of Stroke in the Northern Manhattan Study. *Stroke,* 43**,** 1200-1205.

GARIBALLA, S. & FORSTER, S. 2007. Malnutrition is an independent predictor of 1-year mortality following acute illness. *British Journal of Nutrition,* 98**,** 332-336.

GARIBALLA, S. E., PARKER, S. G., TAUB, N. & CASTLEDEN, C. M. 1998a. Influence of nutritional status on clinical outcome after acute stroke. *American Journal of Clinical Nutrition,* 68**,** 275-281.

GARIBALLA, S. E., PARKER, S. G., TAUB, N. & CASTLEDEN, C. M. 1998b. A randomized, controlled, single-blind trial of nutritional supplementation after acute stroke. *Journal of Parenteral and Enteral Nutrition,* 22**,** 315-319.

GIOLDASIS, G., TALELLI, P., CHRONI, E., DAOULI, J., PAPAPETROPOULOS, T. & ELLUL, J. 2008. In-hospital direct cost of acute ischemic and hemorrhagic stroke in Greece. *Acta Neurol Scand,* 118**,** 268-274.

GOMES, F., HOOKWAY, C. & WEEKES, C. E. 2014. Royal College of Physicians Intercollegiate Stroke Working Party evidence-based guidelines for the nutritional support of patients who have had a stroke. *Journal of Human Nutrition and Dietetics,* 27**,** 107-121.

HA, L., HAUGE, T., SPENNING, A. B. & IVERSEN, P. O. 2010. Individual, nutritional support prevents undernutrition, increases muscle strength and improves QoL among elderly at nutritional risk hospitalized for acute stroke: a randomized, controlled trial. *Clinical Nutrition,* 29**,** 567-73.

HAAST, R. A. M., GUSTAFSON, D. R. & KILIAAN, A. J. 2012. Sex differences in stroke. *J Cereb Blood Flow Metab,* 32**,** 2100-2107.

HAJAT, C., TILLING, K., STEWART, J. A., LEMIC-STOJCEVIC, N. & WOLFE, C. D. A. 2004. Ethnic differences in risk factors for ischemic stroke - A European case-control study. *Stroke,* 35**,** 1562-1567.

HART, C. L., HOLE, D. J. & SMITH, G. D. 2000. Comparison of Risk Factors for Stroke Incidence and Stroke Mortality in 20 Years of Follow-Up in Men and Women in the Renfrew/Paisley Study in Scotland. *Stroke,* 31**,** 1893-1896.

HASSAN, A. E., CHAUDHRY, S. A., JANI, V., GRIGORYAN, M., KHAN, A. A., ADIL, M. M. & QURESHI, A. I. 2013. Is There a Decreased Risk of Intracerebral Hemorrhage and Mortality in Obese Patients Treated with Intravenous Thrombolysis in Acute Ischemic Stroke? *Journal of Stroke and Cerebrovascular Diseases,* 22**,** 545-549.

HENDERSON, S., MOORE, N., LEE, E. & WITHAM, M. D. 2008. Do the malnutrition universal screening tool (MUST) and Birmingham nutrition risk (BNR) score predict mortality in older hospitalised patients? *BMC Geriatr,* 8**,** 26.

HEYMSFIELD, S. B. & CEFALU, W. T. 2013. Does body mass index adequately convey a patient's mortality risk? *JAMA,* 309**,** 87-88.
HIGGINS, J. P. & ALTMAN, D. 2008. Assessing risk of bias in included studies. *In:* HIGGINS, J. P. & GREEN, S. (eds.) *Cochrane hanbook for systematic reviews of interventions.* West Sussex, England: Wiley-Blackwell.
HILL, G. L., PICKFORD, I., YOUNG, G. A., SCHORAH, C. J., BLACKETT, R. L., BURKINSHAW, L., WARREN, J. V. & MORGAN, D. B. 1977. MALNUTRITION IN SURGICAL PATIENTS: An Unrecognised Problem. *The Lancet,* 309**,** 689-692.
HUSAINI, B., LEVINE, R., SHARP, L., CAIN, V., NOVOTNY, M., HULL, P., ORUM, G., SAMAD, Z., SAMPSON, U. & MOONIS, M. 2013. Depression Increases Stroke Hospitalization Cost: An Analysis of 17,010 Stroke Patients in 2008 by Race and Gender. *Stroke research and treatment,* 2013**,** 7.
ISO, H., STAMPFER, M. J., MANSON, J. E., REXRODE, K., HENNEKENS, C. H., COLDITZ, G. A., SPEIZER, F. E. & WILLETT, W. C. 1999. Prospective Study of Calcium, Potassium, and Magnesium Intake and Risk of Stroke in Women. *Stroke,* 30**,** 1772-1779.
JACOBS, E. J., NEWTON, C. C., WANG, Y., PATEL, A. V., MCCULLOUGH, M. L., CAMPBELL, P. T., THUN, M. J. & GAPSTUR, S. M. 2010. Waist Circumference and All-Cause Mortality in a Large US Cohort. *Arch Intern Med,* 170**,** 1293-1301.
JONES, J. M. 2002. The methodology of nutritional screening and assessment tools. *Journal of Human Nutrition and Dietetics,* 15**,** 59-71.
JONES, J. M. 2006. *Nutritional Screening and Assessment Tools,* New York, Nova Science Publishers.
JOONSSON, A. C., LINDGREN, I., NORRVING, B. & LINDGREN, A. 2008. Weight loss after stroke: A population-based study from the Lund Stroke Register. *Stroke,* 39**,** 918-923.
KALANTAR-ZADEH, K., HORWICH, T. B., OREOPOULOS, A., KOVESDY, C. P., YOUNESSI, H., ANKER, S. D. & MORLEY, J. E. 2007. Risk factor paradox in wasting diseases. *Current Opinion in Clinical Nutrition and Metabolic Care,* 10**,** 433-442.
KALM, L. M. & SEMBA, R. D. 2005. They Starved So That Others Be Better Fed: Remembering Ancel Keys and the Minnesota Experiment. *The Journal of Nutrition,* 135**,** 1347-1352.
KERNAN, W. N., INZUCCHI, S. E., SAWAN, C., MACKO, R. F. & FURIE, K. L. 2013. Obesity: A Stubbornly Obvious Target for Stroke Prevention. *Stroke,* 44**,** 278-286.
KIDD, P. M. 2009. Integrated Brain Restoration after Ischemic Stroke - Medical Management, Risk Factors, Nutrients, and other Interventions for Managing Inflammation and Enhancing Brain Plasticity. *Alternative Medicine Review,* 14**,** 14-35.
KIDWELL, C. S., CHALELA, J. A., SAVER, J. L., STARKMAN, S., HILL, M. D., DEMCHUK, A. M., BUTMAN, J. A., PATRONAS, N., ALGER, J. R., LATOUR, L. L., LUBY, M. L., BAIRD, A. E., LEARY, M. C., TREMWEL, M., OVBIAGELE, B., FREDIEU, A., SUZUKI, S., VILLABLANCA, J. P., DAVIS, S., DUNN, B., TODD, J. W., EZZEDDINE, M. A., HAYMORE, J., LYNCH, J. K., DAVIS, L. & WARACH, S. 2004. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. *JAMA,* 292**,** 1823-30.
KIM, B. J., LEE, S.-H., JUNG, K.-H., YU, K.-H., LEE, B.-C., ROH, J.-K. & FOR KOREAN STROKE REGISTRY, I. 2012. Dynamics of obesity paradox after stroke, related to time from onset, age, and causes of death. *Neurology,* 79**,** 856-63.

KIM, B. J., LEE, S. H., RYU, W. S., KIM, C. K., LEE, J. & YOON, B. W. 2011. Paradoxical longevity in obese patients with intracerebral hemorrhage. *Neurology,* 76**,** 567-573.
KLEIN, S., ALLISON, D. B., HEYMSFIELD, S. B., KELLEY, D. E., LEIBEL, R. L., NONAS, C. & KAHN, R. 2007. Waist circumference and cardiometabolic risk: a consensus statement from Shaping America's Health: Association for Weight Management and Obesity Prevention; NAASO, The Obesity Society; the American Society for Nutrition; and the American Diabetes Association. *American Journal of Clinical Nutrition,* 85**,** 1197-1202.
KOVESDY, C. P., ANDERSON, J. E. & KALANTAR-ZADEH, K. 2007. Paradoxical association between body mass index and mortality in men with CKD not yet on dialysis. *American Journal of Kidney Diseases,* 49**,** 581-591.
KREMERS, H. M., NICOLA, P. J., CROWSON, C. S., BALLMAN, K. V. & GABRIEL, S. E. 2004. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. *Arthritis Rheum,* 50**,** 3450-7.
KRUIZENGA, H. M., VAN TULDER, M. W., SEIDELL, J. C., THIJS, A., ADER, H. J. & VAN BOKHORST-DE VAN DER SCHUEREN, M. A. 2005. Effectiveness and cost-effectiveness of early screening and treatment of malnourished patients. *American Journal of Clinical Nutrition,* 82**,** 1082-1089.
LAET, C., KANIS, J. A., ODÉN, A., JOHANSON, H., JOHNELL, O., DELMAS, P., EISMAN, J. A., KROGER, H., FUJIWARA, S., GARNERO, P., MCCLOSKEY, E. V., MELLSTROM, D., MELTON, L. J., 3RD, MEUNIER, P. J., POLS, H. A. P., REEVE, J., SILMAN, A. & TENENHOUSE, A. 2005. Body mass index as a predictor of fracture risk: A meta-analysis. *Osteoporosis International,* 16**,** 1330-1338.
LAMB, C. A., PARR, J., LAMB, E. I. & WARREN, M. D. 2009. Adult malnutrition screening, prevalence and management in a United Kingdom hospital: cross-sectional study. *Br J Nutr,* 102**,** 571-5.
LANDBO, C., PRESCOTT, E., LANGE, P., VESTBO, J. & ALMDAL, T. P. 1999. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med,* 160**,** 1856-61.
LANDI, F., ONDER, G., GAMBASSI, G., PEDONE, C., CARBONIN, P., BERNABEI, R. & GRP ITALIANO, F. A. 2000. Body mass index and mortality among hospitalized patients. *Archives of Internal Medicine,* 160**,** 2641-2644.
LAWLOR, D. A., LEAN, M. & SATTAR, N. 2006. ABC of obesity - Obesity and vascular disease. *British Medical Journal,* 333**,** 1060-1063.
LENNARD-JONES, J. E., ARROWSMITH, H., DAVISON, C., DENHAM, A. F. & MICKLEWRIGHT, A. 1995. Screening by nurses and junior doctors to detect malnutrition when patients are first assessed in hospital *Clinical Nutrition,* 14**,** 336-340.
LIM, S. L., ONG, K. C. B., CHAN, Y. H., LOKE, W. C., FERGUSON, M. & DANIELS, L. 2012. Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. *Clinical Nutrition,* 31**,** 345-350.
MARKUS, H., PEREIRA, A. & CLOUD, G. 2010. *Stroke medicine,* New York, Oxford University Press.
MARKUS, H. S., KHAN, U., BIRNS, J., EVANS, A., KALRA, L., RUDD, A. G., WOLFE, C. D. A. & JERRARD-DUNNE, P. 2007. Differences in Stroke Subtypes Between Black and White Patients With Stroke: The South London Ethnicity and Stroke Study. *Circulation,* 116**,** 2157-2164.

MARTINEAU, J., BAUER, J. D., ISENRING, E. & COHEN, S. 2005. Malnutrition determined by the patient-generated subjective global assessment is associated with poor outcomes in acute stroke patients. *Clinical Nutrition,* 24**,** 1073-1077.

MCWHIRTER, J. P. & PENNINGTON, C. P. 1994. Incidence and recognition of malnutrition in hospital. *British Medical Journal,* 308**,** 945-948.

MEIJERS, J. M., VAN BOKHORST-DE VAN DER SCHUEREN, M. A., SCHOLS, J. M., SOETERS, P. B. & HALFENS, R. J. 2010. Defining malnutrition: mission or mission impossible? *Nutrition,* 26**,** 432-40.

MIDDLETON, M. H., NAZARENKO, G., NIVISON-SMITH, I. & SMERDELY, P. 2001. Prevalence of malnutrition and 12-month incidence of mortality in two Sydney teaching hospitals. *Internal Medicine Journal,* 31**,** 455-461.

MILNE, A. C., POTTER, J., VIVANTI, A. & AVENELL, A. 2009. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane Database of Systematic Reviews***,** CD003288.

MOHAN, K. M., WOLFE, C. D. A., RUDD, A. G., HEUSCHMANN, P. U., KOLOMINSKY-RABAS, P. L. & GRIEVE, A. P. 2011. Risk and Cumulative Risk of Stroke Recurrence: A Systematic Review and Meta-Analysis. *Stroke,* 42**,** 1489-1494.

MORGAN, E. & DENT, M. 2010. The economic burden of obesity. Oxford: National Obesity Observatory.

MOSSELMAN, M. J., KRUITWAGEN, C. L. J. J., SCHUURMANS, M. J. & HAFSTEINSDOTTIR, T. B. 2013. Malnutrition and Risk of Malnutrition in Patients With Stroke: Prevalence During Hospital Stay. *Journal of Neuroscience Nursing,* 45**,** 194-204.

MUREN, M. A., HUTLER, M. & HOOPER, J. 2008. Functional capacity and health-related quality of life in individuals post stroke. *Topics in Stroke Rehabilitation,* 15**,** 51-58.

NATIONAL PATIENT SAFETY AGENCY DYSPHAGIA EXPERT REFERENCE GROUP. 2011. *Dysphagia diet food texture descriptors* [Online]. Available: http://www.bda.uk.com/publications/statements/NationalDescriptorsTextureModificationAdults.pdf [Accessed 1 October 2013].

NDNS 2012. National Diet and Nutrition Survey: Headline Results from Years 1, 2 and 3 (combined) of the Rolling Programme 2008/09 – 2010/11. Department of Health and the Food Standards Agency.

NETER, J. E., STAM, B. E., KOK, F. J., GROBBEE, D. E. & GELEIJNSE, J. M. 2003. Influence of Weight Reduction on Blood Pressure: A Meta-Analysis of Randomized Controlled Trials. *Hypertension,* 42**,** 878-884.

NHS. 2008. Stroke strategy for London. Available: http://www.londonhp.nhs.uk/wp-content/uploads/2011/03/London-Stroke-Strategy.pdf [Accessed 05 March 2012].

NHS. 2013. Statistics on Obesity, Physical Activity and Diet: England, 2013. Available: https://catalogue.ic.nhs.uk/publications/public-health/obesity/obes-phys-acti-diet-eng-2013/obes-phys-acti-diet-eng-2013-rep.pdf [Accessed 15 October 2013].

NICE 2006a. Nutrition Support for Adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition (Clinical Guideline 32). London: National Institute for Health and Clinical Excellence.

NICE 2006b. Obesity - guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. London: National Institute for Health and Clinical Excellence.

NIH. 1999-2010. *National Institutes of Health Stroke Scale International* [Online]. The International Electronic Education Network. Available: http://www.nihstrokescale.org/ 17 September 2010].

NORMAN, K., PICHARD, C., LOCHS, H. & PIRLICH, M. 2008. Prognostic impact of disease-related malnutrition. *Clinical Nutrition,* 27**,** 5-15.

O'DONNELL, M., XAVIER, D., LIU, L., ZHANG, H., CHIN, S. L., RAO-MELACINI, P., RANGARAJAN, S., ISLAM, S., PAIS, P., MCQUEEN, M. J., MONDO, C., DAMASCENO, A., LOPEZ-JARAMILLO, P., HANKEY, G. J., DANS, A. L., YUSOFF, K., TRUELSEN, T., DIENER, H.-C., SACCO, R. L., RYGLEWICZ, D., CZLONKOWSKA, A., WEIMAR, C., WANG, X. & YUSUF, S. 2010. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *The Lancet,* 376**,** 112-123.

OLSEN, T. S., DEHLENDORFF, C., PETERSEN, H. G. & ANDERSEN, K. K. 2008. Body Mass Index and Poststroke Mortality. *Neuroepidemiology,* 30**,** 93-100.

ONAT, A., AVCI, G. S., BARLAN, M. M., UYAREL, H., UZUNLAR, B. & SANSOY, V. 2004. Measures of abdominal obesity assessed for visceral adiposity and relation to coronary risk. *Int J Obes Relat Metab Disord,* 28**,** 1018-25.

OTTERY, F. 2000. Patient generated subjective global assessment *The clinical guideline to oncology nutrition.* American Dietetic Association.

OVBIAGELE, B., BATH, P. M., COTTON, D., VINISKO, R. & DIENER, H.-C. 2011. Obesity and Recurrent Vascular Risk After a Recent Ischemic Stroke. *Stroke,* 42**,** 3397-3402.

OVBIAGELE, B., GOLDSTEIN, L. B., HIGASHIDA, R. T., HOWARD, V. J., JOHNSTON, S. C., KHAVJOU, O. A., LACKLAND, D. T., LICHTMAN, J. H., MOHL, S., SACCO, R. L., SAVER, J. L. & TROGDON, J. G. 2013. Forecasting the Future of Stroke in the United States: A Policy Statement From the American Heart Association and American Stroke Association. *Stroke*.

PARK, Y., PARK, S., YI, H., KIM, H. Y., KANG, S.-J., KIM, J. & AHN, H. 2009. Low level of n-3 polyunsaturated fatty acids in erythrocytes is a risk factor for both acute ischemic and hemorrhagic stroke in Koreans. *Nutrition Research,* 29**,** 825-830.

PENNINGTON, C. R. 1998. Malnutrition in hospital: The case of the stroke patient. *British Journal of Nutrition,* 79**,** 477-478.

PERRY, L. & MCLAREN, S. 2003. Implementing evidence-based guidelines for nutrition support in acute stroke. *Evidence Based Nursing,* 6**,** 68-71.

PISCHON, T., BOEING, H., HOFFMANN, K., BERGMANN, M., SCHULZE, M. B., OVERVAD, K., VAN DER SCHOUW, Y. T., SPENCER, E., MOONS, K. G. M., TJØNNELAND, A., HALKJAER, J., JENSEN, M. K., STEGGER, J., CLAVEL-CHAPELON, F., BOUTRON-RUAULT, M.-C., CHAJES, V., LINSEISEN, J., KAAKS, R., TRICHOPOULOU, A., TRICHOPOULOS, D., BAMIA, C., SIERI, S., PALLI, D., TUMINO, R., VINEIS, P., PANICO, S., PEETERS, P. H. M., MAY, A. M., BUENO-DE-MESQUITA, H. B., VAN DUIJNHOVEN, F. J. B., HALLMANS, G., WEINEHALL, L., MANJER, J., HEDBLAD, B., LUND, E., AGUDO, A., ARRIOLA, L., BARRICARTE, A., NAVARRO, C., MARTINEZ, C., QUIRÓS, J. R., KEY, T., BINGHAM, S., KHAW, K. T., BOFFETTA, P., JENAB, M., FERRARI, P. & RIBOLI, E. 2008. General and Abdominal Adiposity and Risk of Death in Europe. *New England Journal of Medicine,* 359**,** 2105-2120.

POIRIER, P., GILES, T. D., BRAY, G. A., HONG, Y., STERN, J. S., PI-SUNYER, F. X. & ECKEL, R. H. 2006. Obesity and Cardiovascular Disease: Pathophysiology, Evaluation, and Effect of Weight Loss: An Update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease From the Obesity

Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation,* 113**,** 898-918.
RASLAN, M., GONZALEZ, M. C., DIAS, M. C. G., NASCIMENTO, M., CASTRO, M., MARQUES, P., SEGATTO, S., TORRINHAS, R. S., CECCONELLO, I. & WAITZBERG, D. L. 2010. Comparison of nutritional risk screening tools for predicting clinical outcomes in hospitalized patients. *Nutrition,* 26**,** 721-6.
RASLAN, M., GONZALEZ, M. C., TORRINHAS, R. S. M. M., RAVACCI, G. R., PEREIRA, J. C. R. & WAITZBERG, D. L. 2011. Complementarity of Subjective Global Assessment (SGA) and Nutritional Risk Screening 2002 (NRS 2002) for predicting poor clinical outcomes in hospitalized patients. *Clinical Nutrition,* 30**,** 49-53.
RAUTIAINEN, S., LARSSON, S., VIRTAMO, J. & WOLK, A. 2012. Total Antioxidant Capacity of Diet and Risk of Stroke: A Population-Based Prospective Cohort of Women. *Stroke,* 43**,** 335-340.
RCP. 2012. National clinical guideline for stroke (prepared by the Intercollegiate Stroke Working Party). Available: http://www.rcplondon.ac.uk/sites/default/files/national-clinical-guidelines-for-stroke-fourth-edition.pdf [Accessed 4 August 2013].
RILEY, R. D., HIGGINS, J. P. T. & DEEKS, J. J. 2011. Interpretation of random effects meta-analyses. *BMJ,* 342.
RYU, W. S., LEE, S. H., KIM, C. K., KIM, B. J. & YOON, B. W. 2011. Body Mass Index, Initial Neurological Severity and Long-Term Mortality in Ischemic Stroke. *Cerebrovascular Diseases,* 32**,** 170-176.
SAKA, Ö., MCGUIRE, A. & WOLFE, C. 2009. Cost of stroke in the United Kingdom. *Age and Ageing,* 38**,** 27-32.
SCHALLER, B. J., GRAF, R. & JACOBS, A. H. 2006. Pathophysiological changes of the gastrointestinal tract in ischemic stroke. *American Journal of Gastroenterology,* 101**,** 1655-1665.
SCHERBAKOV, N., DIRNAGL, U. & DOEHNER, W. 2011. Body Weight After Stroke: Lessons From the Obesity Paradox. *Stroke,* 42**,** 3646-3650.
SCHLICK, K., RAMAN, R., HEMMEN, T., MEYER, B., MEYER, D., ERNSTROM, K. & OVBIAGELE, B. 2012. Influence of obesity on effectiveness of intravenous tissue-type plasminogen activator in acute ischemic stroke. *Neurology,* Conference**,** Conference Publication: 78 (1 Meeting Abstract).
SCHMIDT, M. I., DUNCAN, B. B., TAVARES, M., POLANCZYK, C. A., PELLANDA, L. & ZIMMER, P. M. 1993. Validity of self-reported weight--a study of urban Brazilian adults. *Revista de Saude Publica,* 27**,** 271-276.
SHETTY, P. 2003. Malnutrition and Undernutrition. *Medicine,* 31**,** 18-22.
SIGN. 2010. Management of patients with stroke: identification and management of dysphagia. A National Clinical Guideline. Available: http://www.sign.ac.uk/pdf/sign119.pdf [Accessed 04 August 2013].
SIZER, T. 1996. Standards and Guidelines for Nutritional Support of Patients in Hospitals. A report by a working party of the British Association for Parenteral and Enteral Nutrition.
SPENCER, E. A., APPLEBY, P. N., DAVEY, G. K. & KEY, T. J. 2002. Validity of self-reported height and weight in 4808 EPIC–Oxford participants. *Public Health Nutrition,* 5**,** 561-565.
SRP. 2001-2003. *The South London Stroke Register (SLSR)* [Online]. London: Stroke Research Programme. Available: http://www.kcl-phs.org.uk/stroke/research/SLSR.htm 2010].

STEWART, J. A., DUNDAS, R., HOWARD, R. S., RUDD, A. G. & WOLFE, C. D. A. 1999. Ethnic differences in incidence of stroke: prospective study with stroke register. *British Medical Journal,* 318**,** 967-971.
STRATTON, R. J. & ELIA, M. 2007. Who benefits from nutritional support: what is the evidence? *European Journal of Gastroenterology & Hepatology,* 19**,** 353-8.
STRATTON, R. J., GREEN, C. J. & ELIA, M. 2003. *Disease-related Malnutrition: An Evidence Based Approach to Treatment,* Wallingford, Oxon, CABI Publishing.
STRATTON, R. J., KING, C. L., STROUD, M. A., JACKSON, A. A. & ELIA, M. 2006. 'Malnutrition Universal Screening Tool' predicts mortality and length of hospital stay in acutely ill elderly. *British Journal of Nutrition,* 95**,** 325-330.
STRAZZULLO, P., D'ELIA, L., CAIRELLA, G., GARBAGNATI, F., CAPPUCCIO, F. P. & SCALFI, L. 2010. Excess Body Weight and Incidence of Stroke Meta-Analysis of Prospective Studies With 2 Million Participants. *Stroke,* 41**,** E418-E426.
SUK, S. H., SACCO, R. L., BODEN-ALBALA, B., CHEUN, J. F., PITTMAN, J. G., ELKIND, M. S. & PAIK, M. C. 2003. Abdominal obesity and risk of ischemic stroke - The Northern Manhattan Stroke Study. *Stroke,* 34**,** 1586-1592.
SULTER, G., STEEN, C. & KEYSER, J. D. 1999. Use of the Barthel Index and Modified Rankin Scale in Acute Stroke Trials. *Stroke,* 30**,** 1538-1541.
TIRSCHWELL, D. L., SMITH, N. L., HECKBERT, S. R., LEMAITRE, R. N., LONGSTRETH, W. T., JR. & PSATY, B. M. 2004. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. *Neurology,* 63**,** 1868-1875.
TOWFIGHI, A. & OVBIAGELE, B. 2009. The Impact of Body Mass Index on Mortality After Stroke. *Stroke,* 40**,** 2704-2708.
TU, J. V., WILLISON, D. J., SILVER, F. L., FANG, J., RICHARDS, J. A., LAUPACIS, A. & KAPRAL, M. K. 2004. Impracticability of Informed Consent in the Registry of the Canadian Stroke Network. *New England Journal of Medicine,* 350**,** 1414-1421.
URETSKY, S., MESSERLI, F. H., BANGALORE, S., CHAMPION, A., COOPER-DEHOFF, R. M., ZHOU, Q. & PEPINE, C. J. 2007. Obesity paradox in patients with hypertension and coronary artery disease. *American Journal of Medicine,* 120**,** 863-870.
VAUTHEY, C., DE FREITAS, G. R., VAN MELLE, G., DEVUYST, G. & BOGOUSSLAVSKY, J. 2000. Better outcome after stroke with higher serum cholesterol levels. *Neurology,* 54**,** 1944-1949.
VEMMOS, K., NTAIOS, G., SPENGOS, K., SAVVARI, P., VEMMOU, A., PAPPA, T., MANIOS, E., GEORGIOPOULOS, G. & ALEVIZAKI, M. 2011. Association Between Obesity and Mortality After Acute First-Ever Stroke The Obesity-Stroke Paradox. *Stroke,* 42**,** 30-36.
VETTA, F., RONZONI, S., TAGLIERI, G. & BOLLEA, M. R. 1999. The impact of malnutrition on the quality of life in the elderly. *Clinical Nutrition,* 18**,** 259-267.
VIVANTI, A. P., CAMPBELL, K. L., SUTER, M. S., HANNAN-JONES, M. T. & HULCOMBE, J. A. 2009. Contribution of thickened drinks, food and enteral and parenteral fluids to fluid intake in hospitalised patients with dysphagia. *Journal of Human Nutrition and Dietetics,* 22**,** 148-155.
VON ELM, E., ALTMAN, D. G., EGGER, M., POCOCK, S. J., GOTZSCHE, P. C. & VANDENBROUCKE, J. P. 2008. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol,* 61**,** 344-9.

WANG, C., LIU, Y., YANG, Q., DAI, X., WU, S., WANG, W., JI, X., LI, L. & FANG, X. 2013. Body mass index and risk of total and type-specific stroke in Chinese adults: results from a longitudinal study in China. *International Journal of Stroke,* 8**,** 245-250.

WANG, G., ZHANG, Z., AYALA, C., DUNET, D. O., FANG, J. & GEORGE, M. G. 2014. Costs of Hospitalization for Stroke Patients Aged 18-64 Years in the United States. *Journal of Stroke and Cerebrovascular Diseases,* 23**,** 861-868.

WANG, L., MANSON, J. E., BURING, J. E., LEE, I.-M. & SESSO, H. D. 2008. Dietary Intake of Dairy Products, Calcium, and Vitamin D and the Risk of Hypertension in Middle-Aged and Older Women. *Hypertension,* 51**,** 1073-1079.

WEEKES, C. E. 2005. *An evaluation of dietetic strategies in the management of chronic obstructive pulmonary disease; nutrition screening, tailored dietary advice and food fortification.* PhD, King's College London (University of London).

WEEKES, C. E. & ELIA, M. 2002. Identifying patients with nutritional problems: A comparison of two nutrition screening tools. *Proceedings of the Nutrition Society,* 61**,** 4A.

WEEKES, C. E., ELIA, M. & EMERY, P. W. 2004. The development, validation and reliability of a nutrition screening tool based on the recommendations of the British Association for Parenteral and Enteral Nutrition (BAPEN). *Clinical Nutrition,* 23**,** 1104-1112.

WESTERGREN, A., KARLSSON, S., ANDERSSON, P., OHLSSON, O. & HALLBERG, I. R. 2001a. Eating difficulties, need for assisted eating, nutritional status and pressure ulcers in patients admitted for stroke rehabilitation. *J Clin Nurs,* 10**,** 257-69.

WESTERGREN, A., KARLSSON, S., ANDERSSON, P., OHLSSON, O. & HALLBERG, I. R. 2001b. Eating difficulties, need for assisted eating, nutritional status and pressure ulcers in patients admitted for stroke rehabilitation. *Journal of Clinical Nursing,* 10**,** 257-267.

WHITE, J. V., GUENTER, P., JENSEN, G., MALONE, A., SCHOFIELD, M., ACADEMY MALNUTRITION WORK GROUP, A.S.P.E.N. MALNUTRITION TASK FORCE & AND THE A.S.P.E.N. BOARD OF DIRECTORS 2012. Consensus Statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: Characteristics Recommended for the Identification and Documentation of Adult Malnutrition (Undernutrition). *Journal of Parenteral and Enteral Nutrition,* 36**,** 275-283.

WHO 2004. The Atlas of Heart Disease and Stroke. Geneva: World Health Organization.

WHO. 2009. *Cardiovascular diseases* [Online]. Geneva: World Health Organization. Available: http://www.who.int/mediacentre/factsheets/fs317/en/index.html].

WHO. 2010. *Nutrition* [Online]. Geneva: World Health Organization. Available: http://www.who.int/topics/nutrition/en/ 2010].

WINTER, Y., ROHRMANN, S., LINSEISEN, J., LANCZIK, O., RINGLEB, P. A., HEBEBRAND, J. & BACK, T. 2008. Contribution of obesity and abdominal fat mass to risk of stroke and transient ischemic attacks. *Stroke; a journal of cerebral circulation,* 39 (12)**,** 3145-3151.

WOLFE, C. & RUDD, T. 2005. The Burden of Stroke White Paper - Raising awareness of the global toll of stroke-related disability and death. Available: http://www.safestroke.org/Portals/10/FINAL%20Burden%20of%20Stroke.pdf [Accessed 15 October 2010].

WOLFE, C. D. 2000. The impact of stroke. *Br Med Bull,* 56**,** 275-86.

WOLFE, C. D. A., SMEETON, N. C., COSHALL, C., TILLING, K. & RUDD, A. G. 2005. Survival differences after stroke in a multiethnic population: follow-up study with the south London stroke register. *British Medical Journal,* 331**,** 431.

WORLD HEALTH ORGANIZATION 2000. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser,* 894**,** i-xii, 1-253.

WORLD HEALTH ORGANIZATION. 2006. *WHO STEPS Stroke Manual: the WHO STEPwise approach to stroke surveillance* [Online]. Geneva. Available: http://www.who.int/chp/steps/Manual.pdf [Accessed 15 September 2013].

WRIGHT, L., COTTER, D., HICKSON, M. & FROST, G. 2005. Comparison of energy and protein intakes of older people consuming a texture modified diet with a normal hospital diet. *Journal of Human Nutrition and Dietetics,* 18**,** 213-219.

YOO, S. H., KIM, J. S., KWON, S. U., YUN, S. C., KOH, J. Y. & KANG, D. W. 2008. Undernutrition as a predictor of poor clinical outcomes in acute ischemic stroke patients. *Archives of Neurology,* 65**,** 39-43.

ZHENG, W., MCLERRAN, D. F., ROLLAND, B., ZHANG, X., INOUE, M., MATSUO, K., HE, J., GUPTA, P. C., RAMADAS, K., TSUGANE, S., IRIE, F., TAMAKOSHI, A., GAO, Y.-T., WANG, R., SHU, X.-O., TSUJI, I., KURIYAMA, S., TANAKA, H., SATOH, H., CHEN, C.-J., YUAN, J.-M., YOO, K.-Y., AHSAN, H., PAN, W.-H., GU, D., PEDNEKAR, M. S., SAUVAGET, C., SASAZUKI, S., SAIRENCHI, T., YANG, G., XIANG, Y.-B., NAGAI, M., SUZUKI, T., NISHINO, Y., YOU, S.-L., KOH, W.-P., PARK, S. K., CHEN, Y., SHEN, C.-Y., THORNQUIST, M., FENG, Z., KANG, D., BOFFETTA, P. & POTTER, J. D. 2011. Association between Body-Mass Index and Risk of Death in More Than 1 Million Asians. *New England Journal of Medicine,* 364**,** 719-729.

ZULIANI, G., CHERUBINI, A., ATTI, A. R., BLÈ, A., VAVALLE, C., DI TODARO, F., BENEDETTI, C., VOLPATO, S., MARINESCU, M. G., SENIN, U. & FELLIN, R. 2004. Low Cholesterol Levels Are Associated With Short-Term Mortality in Older Patients With Ischemic Stroke. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences,* 59**,** M293-M297.

ZWEIG, M. H. & CAMPBELL, G. 1993. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clinical Chemistry,* 39**,** 561-77.

Appendices

Appendix 2.1 – "Nutrition Screening Tool currently used at Guy´s and St Thomas´ NHS Foundation Trust"

11. Nutrition	Completed by (date & initial)

Do you have any special dietary requirements YES / NO **If Yes please specify:-**

Pureed ☐ **Soft** ☐ **Vegetarian** ☐ **Vegan** ☐ **Renal** ☐ **Halal** ☐ **Diabetic** ☐ **Supplement** ☐
Coeliac ☐

Other please specify:-

Do you usually take nutritional supplements? Yes/No **If yes please specify:**

Do you use / need any special equipment to help with eating and drinking e.g. adapted cutlery/plate/cup :-
If yes please specify:-
Feeding cup ☐ **Adapted spoon** ☐ **Adapted knife** ☐ **Adapted fork** ☐ **Adapted plate** ☐

Do you need help with eating and drinking at mealtimes YES / NO
If Yes please specify level of assistance needed

If the patient has any swallowing difficulties, please refer to the Speech and Language therapist
Referral made YES / NO **Date:-**
Swallow Screen YES ☐ **NO** ☐

If patient needs help, please identify with:
a 'red dot' on information white board ☐ **staff informed** ☐ **at meal time use 'red tray'** ☐

NUTRITION SCREENING TOOL
PLEASE COMPLETE RECHECK WITHIN 48 HOURS OF ADMISSION

WEIGHT – Recorded both usual and current weight	Weight the patient and record weight in Kg	
	What is the patient's usual (pre-illness) weight (Kg)?	
HEIGHT – Recorded either recalled or measured height	Recalled i.e. patient – remembered height (^{m})	
	Measured height (^{m}) i.e. using wall-fixed height measure	

Is the Body Mass Index (BMI) less than 18.5 kg/m ^{2}? Check BMI chart
Please circle appropriate response YES / NO

	YES	NO
Has the patient unintentionally lost weight in the last 6 months Score 2 if patient has lost more than 2 kg	2	0
Has the patient unintentionally been eating less in the last 6 months	2	0
Patients who are unable to eat / NBM for more than 5 days need to be referred straight away (irrespective of weight loss or BMI).	4	0
Total Score (please check 'action' once completed)		

Action

Score 0 – 2 Re-assess the patient weekly throughout hospital stay

Score 4 – 6 or BMI less than 18.5 Kg/m ^{2}
or patient on tube feeding or parenteral nutrition
or patient has Grade 3 – 4 pressure sore

Refer to Dietitian for full nutritional assessment

Patient referred to Dietitian YES ☐ **NO** ☐ **Date:-**

NUTRITIONAL WEEKLY MONITORING

Date:	2nd Week		3rd Week		4th Week	
	Weight:		Weight:		Weight:	
Weight loss: If yes, re-check BMI:	Yes: ☐	No: ☐	Yes: ☐	No: ☐	Yes: ☐	No: ☐
Appetite loss / decreased intake:	Yes: ☐	No: ☐	Yes: ☐	No: ☐	Yes: ☐	No: ☐
Art. Feeding / special diet: If yes, specify	Yes: ☐	No: ☐	Yes: ☐	No: ☐	Yes: ☐	No: ☐
Dietetic referral: If yes, date referred	Yes: ☐	No: ☐	Yes: ☐	No: ☐	Yes: ☐	No: ☐
Signature and designation:						

11

Appendix 3.1 – Medline full search strategy

1 exp Stroke/

2 (stroke$ or post?stroke$).ti,ab.

3 ((cerebro$ or brain or cerebral$) adj3 (infarct$ or accident$ or h?emorrhage)).ti,ab.

4 subarachnoid h?emorrhage.ti,ab.

5 1 or 2 or 3 or 4

6 exp Body Mass Index/

7 exp Obesity/

8 body mass index.ti,ab.

9 (obese or obesity or "obesity paradox").ti,ab.

10 6 or 7 or 8 or 9

11 (mortality or death or survival).ti,ab.

12 5 and 10 and 11

13 exp Animal Experimentation/

14 Animals/

15 exp Rodentia/

16 13 or 14 or 15

17 12 not 16

Appendix 3.2 - Multivariable Cox Proportional Hazards Model showing the effect of different variables on 8-year mortality (using ethnicity divided into 3 groups)

	HR	95% CI	*p* value
BMI groups			0.009
Underweight	1.83	1.15-2.90	
Normal weight (reference)	-----	-----	
Overweight	0.89	0.66-1.21	
Type of stroke			0.953
Ischaemic	Reference group	-------	
Haemorrhagic	0.89	0.54-1.43	
Subarachnoid haemorrhage	1.09	0.34-3.59	
Unclassified	0.96	0.51-1.78	
Age (per 1-year increase)	1.06	1.05-1.08	<0.001
Ethnicity			0.027
White	Reference group	-------	
Black	0.64	0.44-0.94	
Other	0.54	0.28-1.07	
Gender (female)	0.79	0.59-1.05	0.099
NIHSS score (per 1-unit increase)	1.07	1.05-1.09	<0.001
Living conditions prior to stroke			0.677
Home	Reference group	-------	
Institutionalized	1.04	0.67-1.63	
Other	0.42	0.57-3.06	
Risk factors			
Hypertension	0.93	0.67-1.28	0.642
CCF	1.58	0.83-3.01	0.168
Angina	0.81	0.51-1.31	0.394
Myocardial infarction	1.13	0.73-1.77	0.585
TIA	1.02	0.65-1.61	0.935
Migraine	0.52	1.25-2.11	0.358
Atrial fibrillation	1.62	1.14-2.29	0.007
Diabetes	1.47	1.03-2.08	0.033
Depression	1.09	0.60-1.97	0.782
Hypercholesterolaemia	0.71	0.51-0.99	0.043

BMI = body mass index; NIHSS = National Institutes of Health Stroke Scale; CCF = congestive cardiac failure; TIA = transient ischaemic attack; HR = hazard ratio.

Appendix 3.3 - Multivariable Cox Proportional Hazards Model showing the effect of different variables on 8-year mortality, adding smoking as a risk factor.

	HR	95% CI	*p* value
BMI groups			0.017
Underweight	1.78	1.12-2.81	
Normal weight (reference)	-----	-----	
Overweight	0.92	0.68-1.24	
Type of stroke			0.987
Ischaemic	Reference group	-	
Haemorrhagic	0.93	0.57-1.52	
Subarachnoid haemorrhage	1.10	0.34-3.59	
Unclassified	0.96	0.52-1.80	
Age (per 1-year increase)	1.07	1.05-1.08	<0.001
Ethnicity			0.224
White	Reference group	-	-
Black Caribbean	0.73	0.47-1.13	
Black African	0.52	0.24-1.14	
Black other	0.67	0.16-2.77	
Other	0.60	0.31-1.19	
Gender (female)	0.82	0.61-1.09	0.177
NIHSS score (per 1-unit increase)	1.07	1.05-1.09	<0.001
Living conditions prior to stroke			0.639
Home	Reference group		
Institutionalized	1.02	0.65-1.60	
Other	0.39	0.05-2.82	
Risk factors			
Hypertension	0.93	0.67-1.28	0.640
CCF	1.64	0.86-3.11	0.135
Angina	0.81	0.50-1.30	0.377
Myocardial infarction	1.14	0.73-1.78	0.572
TIA	1.02	0.65-1.61	0.929
Migraine	0.52	0.13-2.16	0.371
Atrial fibrillation	1.66	1.17-2.36	0.005
Diabetes	1.44	1.01-2.05	0.042
Depression	1.13	0.62-2.05	0.691
Hypercholesterolaemia	0.71	0.51-0.99	0.041
Smoking*	1.20	1.02-1.40	0.026

BMI = body mass index; NIHSS = National Institutes of Health Stroke Scale; CCF = congestive cardiac failure; TIA = transient ischaemic attack; HR = hazard ratio.

*Note: from the 856 patients with available BMI data, 301 (35.2%) never smoked, 286 (33.4%) were ex-smokers, 232 (27.1%) were current smokers and 37 (4.3%) were classified as “unknown”.

Appendix 4.1 – Ethical approval letter

Revised

National Research Ethics Service

NRES Committee Yorkshire & The Humber - Leeds West
First Floor
Millside
Mill Pond Lane
Leeds
LS6 4RA

Telephone: 0113 3050122
Facsimile:

05 May 2011

Dr Elizabeth Weekes
Lead Research Dietician
Guy's & St Thomas' NHS Foundation Trust
St Thomas' Hospital
Westminster Bridge Road
London
SE1 7EH

Dear Dr Weekes

Study title: **Nutritional status after stroke: the relationship between body mass index, central obesity, nutrition risk category and outcome at six months post stroke**
REC reference: **11/YH/0054**

Thank you for your letter of 28 April 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Protocol	2	26 April 2011
REC application		20 February 2011
Response to Request for Further Information		28 April 2011
Participant Information Sheet: Consultee	2	26 April 2011
National Institute of Health Stroke Scale		
Participant Information Sheet	2	26 April 2011
Investigator CV		22 February 2011
Summary/Synopsis	2	26 April 2011
Participant Consent Form	2	26 April 2011
CV for Filomena Gomes		22 February 2011
Screening test for swallowing difficulties		
Consultee declaration form	2	26 April 2011
CV for Professor Emery		21 February 2011
Malnutrition Universal Screening Tool		
Next of kin information letter	1	26 April 2011

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/YH/0054	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Rhona Bratt
Chair

Email: Elaine.hazell@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Karen Ignatian*

Appendix 4.2 – Patient Information Booklet

The association between nutritional status and outcomes after a stroke

REC Reference Number: 11/YH/0054

Can you help with a research project?
We would like to invite you to take part in a research project. Before you decide we would like you to understand why the research is being carried out and what it would involve for you.

One of our team will go through the information booklet with you and answer any questions you have. This should take about 10 – 15 minutes.

Please talk to others about the study if you wish and ask us if anything is not clear.

PART 1

What is the purpose of the study?
The main purpose of the study is to understand if nutritional status is associated with how well people recover after a stroke.
We know overweight people are more likely to have a stroke but we do not know how this influences their recovery after a stroke.
We also know that a person who is thin or has lost weight tends to recover more slowly from many illnesses, but we do not know whether this applies also to people who have had a stroke.

We intend to:

- identify people with a poor nutritional status (thin or losing weight) and see if they have worse outcomes than people with a better nutritional status

- see if the body weight and the distribution of fat increases or decreases the risk of death and the risk of having another stroke

- see if a poor nutritional status affects the hospital costs

Why have I been invited?
You have been invited to take part in this study because we are looking for adults who have had a stroke and have been admitted on the Stroke Units of St. Thomas´ Hospital and King´s College Hospital.

Do I have to take part?
It is up to you to decide if you want to take part in the research. We will describe the study and go through this information booklet with you.

If you agree to take part, we will then ask you to sign a consent form.

You are free to refuse or to withdraw at any time, without giving a reason. This will not affect any of the care you receive.

Who are the researchers?
The research will be conducted by a team based at St Thomas' Hospital and King's College London University:

Dr Elizabeth Weekes, Lead Research Dietitian
Ms Filomena Gomes, Dietitian and PhD student
Prof. Peter Emery, Head of Department of Nutrition and Dietetics

The Chief Investigator is Dr Elizabeth Weekes and this research is being conducted as part of a PhD program for Ms Gomes.

Where will the research take place?
The research will start while you are in hospital and will continue for 6 months after you have been admitted to hospital.

However, you will only be contacted once, while you are in hospital. The follow-up data (regarding your outcomes during these 6 months) will be obtained from a national data warehouse containing details of all admissions to NHS hospitals in England.

What will happen to me if I take part?
If you agree to take part in this study, the researcher (dietitian or research nurse) will take some measurements and ask you (or your carer) some questions that are related to your nutritional status.
You will also be weighed and your height will be measured as part of routine clinical care. If it is not possible for you to stand safely we will obtain information about your weight and height from you, your carers or your medical notes. We will also ask you about your appetite and weight loss in the previous 3 to 6 months. It will take no more than 5 - 10 minutes to make these measurements and collect this information.

The researcher will also measure your waist circumference (with a tape measure around your waist) twice, with you standing (if possible) and lying down on the bed. If you cannot stand, it will only be measured with you comfortably lying down on the bed.
The researcher will then look at your medical records in order to obtain details about type and severity of stroke, medical history and other details such as age, sex and ethnic group.

What will happen after my discharge from hospital?
In order to complete this study we will need to know how well you are recovering 6 months after the stroke.
We will collect information about your outcome from a national data warehouse known as the "Hospital Episode Statistics" (HES). The HES contains details of all hospital admissions to NHS hospital in England including admission and discharge dates, length of hospital stay, diagnosis and survival.
Therefore, as long as you give your consent, we will legally obtain this information directly, without the need to contact you again. This will avoid any inconvenience to you.

What do I need to do?
Once you have left hospital we will not contact you again to obtain more information from you.

Why is this research important?
This research is important because it will help us to understand:

- if it is possible to identify people who are likely to recover more slowly from a stroke because they are thin or have lost weight
- whether a particular body shape (including amount and distribution of fat in the body) is protective or harmful after a stroke
- whether a patient who is thin or has lost weight costs more to treat in the NHS than someone who is well-nourished

Are there any benefits to taking part?
We cannot promise the study will help you, but the information we get from this research may help to improve health care practices in the future and consequently help to improve outcomes of patients who have had a stroke.

Your medical treatment will not be affected by taking part in this study. We do not expect the study to cause you any pain, discomfort or distress.

What will happen when the research is finished?
A summary of the results will be available and we will send you a copy if you request it.
The results of the research will be published in reports and will be presented at conferences. The research may also be used for teaching purposes.

Any information presented about you will be done in a way so that you cannot be recognised i.e. your name and address will be removed.

PART 2

What will happen if I don't want to carry on in the study?
You are free to stop the research at any time and you do not have to give a reason why. We will not collect any more information about you after that time.

If you stop the research before the study is finished, we would like your permission to use the information we have already collected.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researchers. They will do their best to answer your questions. Their contact details are on the last page of this booklet.

If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS).
Patient Advice and Liaison Service
KIC, Ground Floor, North Wing,
St Thomas' Hospital,
Westminster Bridge Road,
London SE1 7EH
Tel: 0207 188 8801 or 0207 188 8803
Email: pals@gstt.nhs.uk

Patient Advice and Liaison Service
King's College Hospital
Denmark Hill
London, SE5 9RS
Tel: 020 3299 3625 / 020 3299 3601
Email: kch-tr.PALS@nhs.net.

This trial is sponsored by Guy's and St Thomas' NHS Foundation Trust. All professional staff involved in the study hold professional indemnity to work within Guy's and St Thomas' NHS Foundation Trust. In the event that you are harmed during the research and this is due to negligence then you may have grounds for legal action for compensation against Guy's and St Thomas NHS Trust but you may have to pay your legal costs. The normal NHS complaints mechanisms are still available to you.

What will happen to the information we collect?
The Chief Investigator (Dr Elizabeth Weekes) will be responsible for ensuring that all the information we collect about you during the study will be kept strictly confidential.

All the information we collect and receive (after obtaining the required approvals) will be stored on a password protected computer, specifically purchased for this purpose. Only members of the research team will have access to information we collect during the study.

Any information about you which leaves the hospital will have your personal details removed so that you cannot be recognised.

Contact details
If you have any questions about the study please talk to one of the researchers:

Chief Investigator
Dr Elizabeth Weekes
Clinical Expert in Disease-Related Malnutrition and Research Lead
Department of Nutrition and Dietetics
St Thomas' Hospital
Westminster Bridge Road
London
SE1 7EH
Tel: 0207 188 2014 (direct line)
E-mail: elizabeth.weekes@gstt.nhs.uk

Ms Filomena Gomes,
Dietitian and PhD student
Diabetes and Nutritional Sciences Division
School of Medicine
King's College London
Franklin Wilkins Building - Room 4.46
150 Stamford Street
London SE1 9NH
Tel: 020 7848 4594
E-mail: filomena.gomes@kcl.ac.uk

Prof Peter Emery
Head of Department of Nutrition and Dietetics
King's College London
Franklin-Wilkins Building
150 Stamford Street
London SE1 9NH
Tel: 020-7848-4415
Fax: 020-7848-4500
E-mail: peter.emery@kcl.ac.uk

Appendix 4.3 – Consent form

Guy's and St Thomas' NHS
NHS Foundation Trust

"The association between nutritional status and outcomes after a stroke"
Consent Form

REC Reference Number: 11/YH/0054 **Chief Investigator:** Dr Elizabeth Weekes

Patient ID number for this study ....

Please initial box

1. I confirm that I have read and understand the information booklet dated 26th April 2011 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals in the research team, from regulatory authorities or from the NHS Trust, where it is relevant to taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that information held by the NHS and records maintained by The NHS Information Centre and/or the NHS Central Register may be used to provide information about my health status. ☐

5. I agree to take part in the above study. ☐

____________________	________________________	_____________
Name of patient	Signature	Date
____________________	________________________	_____________
Name of person taking consent	Signature	Date

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes

The association between nutritional status and outcomes after a stroke PROTOCOL v2 - 26th April, 2011

Appendix 4.4 – Consultee declaration form

Guy's and St Thomas' NHS
NHS Foundation Trust

"The association between nutritional status and outcomes after a stroke"
Consultee declaration form

REC Reference Number: 11/YH/0054

Chief Investigator: Dr Elizabeth Weekes

Patient ID number for this study ....

Please initial box

1.	I .... have been consulted about ....'s participation in this research project. I have had the opportunity to ask questions about the study and understand what is involved.	☐
2.	In my opinion he/she would have no objection to taking part in the above study.	☐
3.	I understand that I can request he/she is withdrawn from the study at any time, without giving any reason and without his/her care or legal rights being affected.	☐
4.	I understand that relevant sections of his/her care record and data collected during the study may be looked at by individuals in the research team, from regulatory authorities or from the NHS Trust, where it is relevant to their taking part in this research.	☐
5.	I understand that information held by the NHS and records maintained by The NHS Information Centre and/or the NHS Central Register may be used to provide information about his/her health status.	☐

____________________	____________________	______________________
Name of consultee Relationship to participant:	Date	Signature
____________________	____________________	______________________
Person undertaking consultation (if different from researcher)	Date	Signature
____________________	____________________	______________________
Researcher	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes

Appendix 4.5 – Next of kin information letter

Guy's and St Thomas' NHS
NHS Foundation Trust

Department of Nutrition & Dietetics
St Thomas' Hospital
Westminster Bridge road
London
SE1 7EH
Tel: 0207 188 2014 (direct line)
Email: elizabeth.weekes@gstt.nhs.uk

Dear

REC Reference Number: 11/YH/0054
Study title: "The association between nutritional status and outcomes after a stroke"

Your relative/friend, ______________________ (date of birth dd/mm/yyyy) took part in the above study while they were in hospital following a stroke.

This letter confirms the following details regarding their participation in the study:

- The patient gave formal written consent to participate in this study
- The baseline data were collected while the patient was in hospital.
- The follow-up data will be collected 6 months after hospital admission. The data will be collected from a national data warehouse (the Hospital Episode Statistics) which is an electronic database that contains details of all hospital admissions in England.
- There will be no need to contact the patient again after discharge from hospital.

If you have any queries regarding this study please contact me (the Chief Investigator) at the above address.

Yours sincerely,

EWeekes

Elizabeth Weekes PhD RD
Consultant Dietitian and Research Lead
Guy's & St Thomas' NHS Foundation Trust

Nutritional status after stroke PROTOCOL v1 (26/04/2011)

Appendix 4.6 – Data collection sheet

Data Collection Sheet

"The association between nutritional status and outcomes after a stroke"

Date of data collection:____/____/____ (dd/mm/yyyy) **Admission date:** ____/____/____

Study ID number:________ **Date of stroke:** ____/____/____

Gender

M___ F ___

Ethnic group

White ___
Black ___
East Asian ___
South Asian ___
Mixed ethnic background ___
Any other background ___

Type of stroke

Ischemic stroke ___
Intracer. Haemorrhage ___
Subarac. Haemorrhage ___
Unclassified ___

Living conditions prior to stroke

Home (unsupported) ___
Home (with support) ___
Institutionalized ___
Other ___

Medical History

Hypertension ___
Diabetes ___
Dislipidemia ___
Smoking ___
Ischaemic heart disease ___
Heart failure ___
Atrial fibrillation ___
Previous TIA ___
Heavy alcohol consumption ___

GI diseases ___
Cognitive dysfunction ___
Impaired mobility ___

Previous stroke

Yes: ___

>1y ago ___
<1y ago ___

No: ___

Severity of stroke

NIHSS score ___
Not assessed ___

Swallow test

Failed ___
Passed ___
Not assessed ___

Patient' height

_ . _ _ m

Measured ___
Recalled ___

If the patient is unable to stand and do not know the height, please measure the ulna length:
_ _ cm

Patient' current weight

_ _ _ . _ Kg

Patient' usual weight
(6M ago, if possible)

_ _ _ . _ Kg

How was weight obtained?

Measured ___

Impossible to measure?

Recalled by patient/relative ___
Medical records ___

Body Mass Index

$\frac{\text{Weight}}{(\text{Height})^2}$ = _ _ . _ kg/m^2

Malnutrition Universal Screening Tool

BMI (kg/m^2) Score
>20 = 0
18.5 -20 = 1
<18.5 = 2

Unintentional weight loss in the past 3-6 months:
% Score
<5 = 0
5-10 = 1
>10 = 2

If patient is acutely ill **and** there has been or is likely to be no nutritional intake for >5 days ⇨ Score 2

Add scores together to calculate overall risk of malnutrition:

___ Score 0 - Low Risk
___ Score 1 - Medium Risk
___ Score 2 or more - High Risk

If impossible to undertake any of these measurements, please describe why:

Nutrition Screening Tool from Guy´s and St Thomas´ Hospitals

Unintentional weight loss in the past 6 months
Yes = 2
No = 0

Loss of appetite/decrease in dietary intake in the last 6 months
Yes = 2
No = 0

Inability to eat/nil by mouth (NBM) for more than 5 days
Yes = 4
No = 0

If patient has a BMI less than 18.5 kg/m^2 ⇨ Score 4

Add scores together to calculate overall risk of malnutrition:

___ Score 0 - Low Risk
___ Score 2 - Medium Risk
___ Score 4 or more - High Risk

If impossible to undertake any of these measurements, please describe why:

____

Waist circumference
(measured at the midpoint between the lower border of the rib cage and the iliac crest):

Patient standing and relaxed __ __ __ cm
Patient lying down __ __ __ cm
(take both measurements in as many patients as possible)

Impossible to measure ___

Appendix 4.7 – National Institutes of Health Stroke Scale

National Institutes of Health Stroke Scale

Item	Scoring		On admission	24 hrs
1a. Level of Consciousness	Alert and responsive – 0 Not alert but arousable by minor stimulation to attend – 1 Not alert requires repeated stimulation to attend – 2 Unresponsive - 3			
1b. LOC questions – month and age	Answers both correctly – 0 Answers one correctly – 1 Answers neither correctly - 2			
1c. LOC commands – open and close eyes and make fist	Performs both correctly – 0 Performs one correctly – 1 Performs neither correctly - 2			
2. Best Gaze	Normal – 0 Partial gaze palsy – 1 Forced deviation or gaze paresis not overcome by oculocephalic movement - 2			
3. Visual fields	No visual loss – 0 Partial hemianopia – 1 Complete hemianopia – 2 Bilateral hemianopia(including cortical blindness) - 3			
4. Facial palsy	Normal – 0 Minor facial paresis – 1 Partial facial paresis (total or near total of lower face) – 2 Complete paralysis of one or both sides (absence of facial movement in upper and lower face) - 3			
5. Motor arm	No drift – 0 Drift (10 secs) – 1 Some effort against gravity (limb cannot get to or maintain 90 degrees) – 2 No effort against gravity (limb falls) – 3 No movement – 4 Amputation/joint fusion - 9	Right		
		Left		
6. Motor leg	No drift – 0 Drift (5 secs) – 1 Some effort against gravity (limb cannot get to or maintain 90 degrees) – 2 No effort against gravity – 3 No movement – 4 Amputation/joint fusion - 9	Right		
		Left		
7. Limb ataxia	Absent – 0 Present in one limb – 1 Present in two limbs – 2			
8. Sensory	Normal no sensory loss – 0 Mild to moderate sensory loss – 1 Severe to total sensory loss - 2			
9. Language	No aphasia, normal – 0 Mild to moderate aphasia – 1 Severe aphasia – 2 Mute - 3			
10. Dysarthria	Normal articulation – 0 Mild to moderate slurring – 1 Severe or unintelligible(mute or anathric) – 2 Intubated or other physical barrier - 9			
11. Extinction and inattention (neglect) – if hemianopia present score at least 1	No abnormality – 0 Inattention to one modality – 1 Inattention to two or more modalities - 2			
	TOTAL			

Appendix 4.8 – Swallow screening test

Please Complete or Affix label

Surname:

Forename:

Date of Birth:

Hospital No: NHS No:

Guy's and St Thomas' NHS
NHS Foundation Trust

Ward:

Sheet No:

SWALLOW TEST

A screening test for swallowing difficulties to be used by doctors and nurses within 12 hours of patient admission and repeat every 24 hours if patient fails the test and Speech/Language Therapist (SALT) is unavailable
N.B. DO NOT ATTEMPT THE TEST IF PATIENT IS DROWSY AND DOES NOT OPEN EYES TO SPEECH, OR IS DROOLING - KEEP NIL BY MOUTH.

1: IF PATIENT IS ALERT AND CAN BE SAT UPRIGHT, GIVE A TEASPOON OF WATER x 3.
Place fingers midline above and below larynx and feels the swallow. After each teaspoon note signs. →

SIGNS		
Absent swallow	Y	N
Cough/delayed cough (up to 2 min, after swallow)	Y	N
Wet voice	Y	N

YES to any signs observed → Keep NIL BY MOUTH and refer to speech language therapy

↓

If NO signs observed then continue:

↓

2. CONTINUOUSLY DRINK A THIRD OF A GLASS OF WATER →

SIGNS		
Absent swallow	Y	N
Cough/delayed cough (up to 2 min, after swallow)	Y	N
Wet voice	Y	N

YES to any signs observed → Keep NIL BY MOUTH and refer to speech language therapy

↓

If NO signs observed continue: → START NORMAL FEEDING WITH CAUTION (continue to observe for swallowing difficulties such as coughing or development of a chest infection.)

OUTCOME	
NBM refer to SALT	☐
Normal Feeding	☐

Signed:

Designation:

Print:

Date: Time:

*Please file this form in Patient Records

High Risk Patients

1.* Neurological: Acute CVA, head injury, post neurosurgery, Guillain Barre Progressive: eg MND, PD, MS, advanced dementia, AIDS

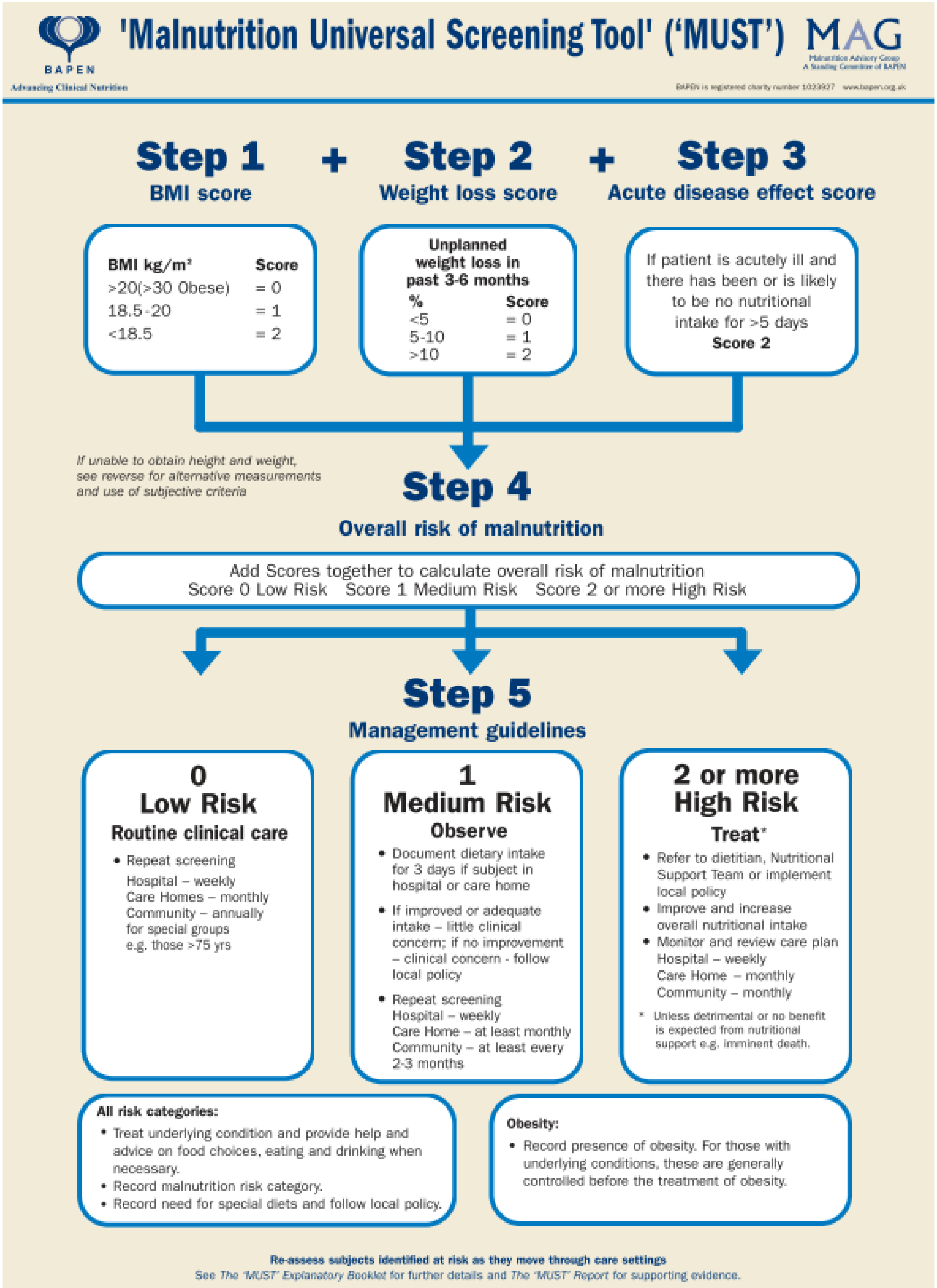
2.* Structural: Post oral or neck surgery, tracheostomy, oesophageal or pharyngeal stricture

3.* Others: Others: - post head/neck radiotherapy, HIV/AIDS, recurrent chest infections, drugs.

N.B. THIS SWALLOW TEST WILL NOT DETECT PATIENTS who only have difficulties swallowing solids e.g. those with structural difficulties. Consider whether a modified diet is required and refer to Speech and Language Therapist if concerned.

WVG 981

Appendix 4.9 – Malnutrition universal Screening Tool (reproduced from www.bapen.org.uk/pdfs/must/must_full.pdf)



Appendix 4.10 – Fields requested to Hospital Episode Statistics

The following fields were requested for all episodes occurring in 2011/12 and 2012/13:

- Patient unique identifier
- Date of admission
- Method of admission
- Date of discharge
- Destination on discharge
- Method of discharge
- Bed days within the year
- Beginning of spell
- Date episode ended
- Date episode started
- Duration of spell
- End of spell
- Episode duration
- Episode order
- Episode status
- Episode type
- Hospital provider spell number
- Ward type at start of episode
- Discharge ready date
- All diagnoses codes
- Primary diagnoses
- Dominant procedure
- NHS-generated Healthcare Resource Group code
- NHS-generated Healthcare Resource Group code version number
- SUS generated core spell Healthcare Resource Group
- SUS generated Healthcare Resource Group
- SUS generated Healthcare Resource Group version number
- SUS generated spell ID

Appendix 4.11

a) Multivariable Cox Proportional Hazards Model showing the effect of different variables on 6-month mortality, including BMI:

	HR	95% CI	*p* value
BMI groups			0.057
Underweight	0.82	0.41-1.65	0.58
Normal weight (reference)	-----	-----	-----
Overweight	0.57	0.33-0.97	0.038
Obese	0.46	0.24-0.88	0.02
Age	1.06	1.03-1.09	<0.001
Gender	1.27	0.82-1.97	0.288
Ethnicity	0.80	0.54-1.19	0.271
Type of stroke	1.27	0.69-2.31	0.429
Severity of stroke	1.13	1.09-1.16	<0.001
Risk factors			
Hypertension	1.82	1.07-3.09	0.026
Diabetes	1.36	0.78-2.32	0.268
Dyslipidemia	0.64	0.39-1.06	0.082
Smoking	1.79	0.84-3.84	0.134
IHD	1.94	1.15-3.26	0.013
Heart failure	4.02	1.92-8.44	<0.001
Atrial fibrillation	1.05	0.67-1.64	0.835
Previous TIA	1.15	0.61-2.18	0.658
Heavy alcohol consumption	0.95	0.28-3.19	0.930

b) Multivariable Cox Proportional Hazards Model showing the effect of different variables on 6-month mortality, including WC:

	HR	95% CI	*p* value
WC quartiles			0.107
1st quartile (reference)	-----	-----	-----
2nd quartile	0.64	0.37-1.09	0.103
3rd quartile	0.60	0.33-1.06	0.080
4th quartile	0.52	0.29-0.94	0.031
Age	1.07	1.04-1.09	<0.001
Gender	1.24	0.81-1.90	0.325
Ethnicity	0.80	0.54-1.19	0.278
Type of stroke	1.30	0.72-2.37	0.388
Severity of stroke	1.13	1.09-1.17	<0.001
Risk factors			
Hypertension	1.78	1.05-3.03	0.033
Diabetes	1.30	0.76-2.21	0.335
Dyslipidemia	0.67	0.41-1.09	0.111
Smoking	1.79	0.83-3.88	0.140
IHD	1.74	1.05-2.89	0.033
Heart failure	3.56	1.72-7.36	0.001
Atrial fibrillation	1.06	0.68-1.65	0.794
Previous TIA	1.17	0.62-2.20	0.621
Heavy alcohol consumption	1.03	0.30-3.49	0.965

c) Multivariable Cox Proportional Hazards Model showing the effect of different variables on 6-month mortality, including risk of malnutrition as determined by the GSTT NST:

	HR	95% CI	*p* value
Risk of malnutrition			<0.001
Low risk	-----	-----	-----
Medium risk	2.1	0.87-5.09	0.099
High risk	5.99	3.42-10.50	<0.001
Age	1.06	1.03-1.09	<0.001
Gender	1.25	0.81-1.92	0.314
Ethnicity	0.79	0.54-1.17	0.237
Type of stroke	1.31	0.72-2.42	0.378
Severity of stroke	1.09	1.06-1.13	<0.001
Risk factors			
Hypertension	1.95	1.14-3.33	0.014
Diabetes	1.36	0.79-2.32	0.257
Dyslipidemia	0.72	0.43-1.18	0.190
Smoking	1.52	0.69-3.32	0.298
IHD	1.73	1.04-2.88	0.035
Heart failure	3.28	1.60-6.73	0.001
Atrial fibrillation	1.10	0.71-1.70	0.678
Previous TIA	1.39	0.73-2.62	0.315
Heavy alcohol consumption	1.27	0.37-4.37	0.704

d) Multivariable Cox Proportional Hazards Model showing the effect of different variables on 6-month mortality, including risk of malnutrition as determined by the MUST:

	HR	95% CI	*p* value
Risk of malnutrition			<0.001
Low risk	-----	-----	-----
Medium risk	3.77	1.71-8.31	0.001
High risk	5.58	3.24-9.64	<0.001
Age	1.06	1.03-1.09	<0.001
Gender	1.31	0.85-2.02	0.229
Ethnicity	0.89	0.61-1.30	0.540
Type of stroke	1.21	0.67-2.20	0.529
Severity of stroke	1.09	1.05-1.13	<0.001
Risk factors			
Hypertension	2.23	1.31-3.82	0.003
Diabetes	1.34	0.79-2.28	0.270
Dyslipidemia	0.70	0.42-1.15	0.154
Smoking	1.72	0.77-3.85	0.188
IHD	1.79	1.07-2.97	0.026
Heart failure	3.19	1.54-6.62	0.002
Atrial fibrillation	1.13	0.73-1.76	0.584
Previous TIA	1.49	0.79-2.83	0.220
Heavy alcohol consumption	0.98	0.28-3.42	0.972

Appendix 4.12 – Rates of mortality and risk of mortality according to groups of BMI and quartiles of WC, using univariate and multivariable Cox Proportional Hazards Models, for the subgroup of patients with ischaemic strokes.

	n	Mortality rates (Chi-square test)	Univariate Cox Proportional Hazards Model		Multivariable* Cox Proportional Hazards Model	
			Hazard ratio	**95% CI**	**Hazard ratio**	**95% CI**
Body Mass Index categories	472	*p=0.003*	*p=0.001*		*p=0.100*	
Underweight (<18.5 kg/m^2)	33	30.3%	1.25	0.64-2.54	0.85	0.41-1.78
Normal weight (18.5-24.9 kg/m^2)	175	23.4%	Reference group		Reference group	
Overweight (25-29.9 kg/m^2)	157	12.1%	0.48	0.28-0.82	0.57	0.32-1.02
Obesity (>30 kg/m^2)	107	11.2%	0.43	0.23-0.82	0.49	0.25-0.95
Waist Circumference Quartiles	471	*p=0.172*	*p=0.176*		*p=0.257*	
1st quartile	121	24.0%	Reference group		Reference group	
2nd quartile	124	16.1%	0.65	0.37-1.15	0.7	0.39-1.25
3rd quartile	117	14.5%	0.58	0.32-1.06	0.62	0.33-1.15
4th quartile	109	14.7%	0.57	0.31-1.05	0.56	0.30-1.06

*adjusted for age, gender, ethnicity, type and severity of stroke (NIHSS score) + 9 stroke risk factors: HT, diabetes, dyslipidemia, smoking, IHD, heart failure, AF, previous TIA and heavy alcohol consumption

Appendix 4.13 – Rates of mortality and risk of mortality according to groups of risk of malnutrition, using univariate and multivariable Cox Proportional Hazards Models, for the subgroup of patients with ischaemic strokes.

	n	Mortality rates (Chi-square test)	Univariate Cox Proportional Hazards Model		Multivariable [a] Cox Proportional Hazards Model	
			Hazard Ratio	95% CI	Hazard Ratio	95% CI
Guy's and St. Thomas' Nutrition Screening Tool	472	*p<0.001*	*p<0.001*		*p<0.001*	
Low risk	280	5.7%	Reference group		Reference group	
Medium risk	49	12.2%	2.25	0.88-5.74	1.85	0.72-4.74
High risk	143	42.0%	9.57	5.51-16.62	5.56	3.08-10.03
Malnutrition Universal Screening Tool	467	*p<0.001*	*p<0.001*		*p<0.001*	
Low risk	303	5.9%	Reference group		Reference group	
Medium risk	32	25.0%	4.75	2.06-10.92	3.69	1.58-8.63
High risk	132	42.4%	9.31	5.47-15.84	5.64	3.17-10.11

[a] - adjusted for age, gender, ethnicity, type and severity of stroke (NIHSS score) + 9 stroke risk factors: HT, diabetes, dyslipidemia, smoking, IHD, heart failure, AF, previous TIA and heavy alcohol consumption

Appendix 4.14 - Rates of mortality and risk of mortality according to groups of BMI and quartiles of WC, using univariate and multivariable Cox Proportional Hazards Models, for the subgroup of patients aged 65 and older.

	n	Mortality rates (Chi-square test)	Univariate Cox Proportional Hazards Model		Multivariable [a] Cox Proportional Hazards Model	
			Hazard ratio	95% CI	Hazard ratio	95% CI
Body Mass Index categories	434	*p=0.020*	*p=0.021*		*p=0.181*	
Underweight (<18.5 kg/m^2)	33	33.3%	1.26	0.65-2.44	0.9	0.44-1.81
Normal weight (18.5-24.9 kg/m^2)	179	25.7%	Reference group		Reference group	
Overweight (25-29.9 kg/m^2)	139	15.8%	0.56	0.34-0.94	0.66	0.38-1.15
Obesity (>30 kg/m^2)	83	14.5%	0.51	0.27-0.95	0.51	0.26-0.99
Waist Circumference Quartiles	433	*p=0.145*	*p=0.133*		*p=0.291*	
1st quartile	117	28.2%	Reference group		Reference group	
2nd quartile	108	20.4%	0.69	0.40-1.18	0.71	0.41-1.22
3rd quartile	111	17.1%	0.57	0.32-1.00	0.66	0.37-1.22
4th quartile	97	17.5%	0.57	0.32-1.02	0.58	0.31-1.07

a - adjusted for age, gender, ethnicity, type and severity of stroke (NIHSS score) + 9 stroke risk factors: HT, diabetes, dyslipidemia, smoking, IHD, heart failure, AF, previous TIA and heavy alcohol consumption

Appendix 4.15 - Rates of mortality and risk of mortality according to groups of risk of malnutrition, using univariate and multivariable Cox Proportional Hazards Models, for the subgroup of patients aged 65 and older.

	n	Mortality rates (Chi-square test)	Univariate Cox Proportional Hazards Model		Multivariable [a] Cox Proportional Hazards Model	
			Hazard Ratio	95% CI	Hazard Ratio	95% CI
Guy's and St. Thomas' Nutrition Screening Tool	434	*p<0.001*	*p<0.001*		*p<0.001*	
Low risk	238	5.7%	Reference group		Reference group	
Medium risk	40	12.2%	1.8	0.67-4.89	1.49	0.55-4.05
High risk	156	42.0%	8.28	4.87-14.09	5.46	3.10-9.61
Malnutrition Universal Screening Tool	429	*p<0.001*	*p<0.001*		*p<0.001*	
Low risk	255	5.9%	Reference group		Reference group	
Medium risk	34	25.0%	3.9	1.76-8.61	3.39	1.47-7.79
High risk	140	42.4%	8.09	4.84-13.52	5.4	3.08-9.47

[a] - adjusted for age, gender, ethnicity, type and severity of stroke (NIHSS score) + 9 stroke risk factors: HT, diabetes, dyslipidemia, smoking, IHD, heart failure, AF, previous TIA and heavy alcohol consumption

Appendix 4.16

a) Association between risk of malnutrition as defined by the GSTT NST and ranked length of hospital stay, adjusted for the effect of several covariates (univariate analysis of variance)

Predictor variable	**F**	***p* value**
Risk of malnutrition (GSTT NST score)	17.96	<0.001
Gender	0.10	0.753
Ethnicity	0.31	0.578
Severity of stroke	121.45	<0.001
Type of stroke	16.11	<0.001
Age	9.72	0.002
Hypertension	0.68	0.409
Diabetes	5.61	0.018
Dyslipidemia	0.00	0.962
Smoking	3.21	0.074
IHD	0.50	0.479
Heart failure	1.95	0.163
Atrial fibrillation	0.01	0.938
Previous TIA	0.37	0.546
Heavy alcohol consumption	0.04	0.846

b) Association between risk of malnutrition as defined by the MUST and ranked length of hospital stay, adjusted for the effect of several covariates (univariate analysis of variance)

Predictor variable	F	*p* value
Risk of malnutrition (MUST score)	18.40	<0.001
Gender	0.14	0.708
Ethnicity	0.06	0.800
Severity of stroke	115.77	<0.001
Type of stroke	13.43	<0.001
Age	8.07	0.005
Hypertension	1.04	0.309
Diabetes	5.63	0.018
Dyslipidemia	0.06	0.805
Smoking	3.12	0.078
IHD	0.96	0.327
Heart failure	3.92	0.048
Atrial fibrillation	0.03	0.872
Previous TIA	0.26	0.610
Heavy alcohol consumption	0.14	0.712

Appendix 4.17 - Length of hospital stay of patients who survived a 6 months, according to groups of BMI and quartiles of WC (unadjusted and adjusted results)

		n	Median	Min-Max	Kruskal -Wallis test (p-value)	Univariate analysis of variance [a] (p values)
BMI (n=448)	**Underweight**	27	20	2-194	0.348	0.439
	Normal weight	157	24	2-165		
	Overweight	155	18	2-174		
	Obese	109	17	2-167		
WC (n=447)	**1st quartile**	107	19	2-194	0.655	0.896
	2nd quartile	117	15	2-155		
	3rd quartile	113	18	2-174		
	4th quartile	110	22	2-167		

[a] - adjusted for age, gender, ethnicity, type and severity of stroke (NIHSS score)

Appendix 4.18

a) Association between risk of malnutrition as defined by the GSTT NST and ranked hospitalisation costs, adjusted for the effect of several covariates (univariate analysis of variance)

Predictor variable	**F**	***p* value**
Risk of malnutrition (GSTT NST score)	9.03	<0.001
Gender	1.70	0.193
Ethnicity	0.83	0.362
Severity of stroke	81.19	<0.001
Type of stroke	6.94	0.009
Age	2.90	0.089
Hypertension	0.15	0.698
Diabetes	4.24	0.040
Dyslipidemia	0.61	0.435
Smoking	0.80	0.373
IHD	0.33	0.569
Heart failure	4.80	0.029
Atrial fibrillation	0.64	0.423
Previous TIA	0.12	0.733
Heavy alcohol consumption	0.64	0.424

b) Association between risk of malnutrition as defined by the MUST and ranked hospitalisation costs, adjusted for the effect of several covariates (univariate analysis of variance)

Predictor variable	**F**	***p* value**
Risk of malnutrition (MUST score)	9.52	<0.001
Gender	1.65	0.199
Ethnicity	0.19	0.660
Severity of stroke	77.66	<0.001
Type of stroke	5.24	0.023
Age	2.44	0.119
Hypertension	0.28	0.596
Diabetes	4.79	0.029
Dyslipidemia	0.31	0.575
Smoking	0.46	0.498
IHD	0.81	0.368
Heart failure	6.44	0.012
Atrial fibrillation	1.01	0.316
Previous TIA	0.06	0.808
Heavy alcohol consumption	1.02	0.313

Appendix 4.19 - Hospitalisation costs of patients at 6 months post-stroke, according to groups of BMI and quartiles of WC

		n	Median £ (min-max)	Kruskal-Wallis test (p-value)	Univariate analysis of variance [a] (p values)
Body mass index (n=446)	**underweight**	27	**7544** (552-21843)	0.729	0.733
	normal weight	156	**6175** (437-27171)		
	overweight	154	**6576** (537-38245)		
	obese	109	**5260** (715-31905)		
Waist circumference (n=445)	**1st quartile**	106	**5247** (437-21843)	0.713	0.962
	2nd quartile	117	**5968** (537-27171)		
	3rd quartile	113	**6080** (739-38245)		
	4th quartile	109	**6978** (552-31905)		

[a] - adjusted for age, gender, ethnicity, type and severity of stroke (NIHSS score)

Appendix 4.20 - Reasons for pre-stroke unintentional weight loss, as reported by patients, their relatives/carers and medical notes

a) Disease-related reasons:

"Swallowing problems since last stroke"

"Swallowing problems since throat cancer"

"Due to my illness"

"Stomach upset for months"

"She has gradually becoming less mobile and does not prepare her meals"

"Sometimes does not eat for days at time due to binge drinking"

"Due to excessive alcohol intake"

"I have been anxious about eating and opening my bowels (because of my diverticular *disease)"*

"I have been hospitalized for a long period of time"

"Due to recent frequent hospital admissions" (testimonial from a patient with a high fall risk)

"Due to diarrhoea as a consequence of antibiotic use for a chest infection in a recent *hospital admission"*

"Due to gastric surgery and pneumonia in the last 3 months"

"Vomiting and eating too little, no appetite during 2 weeks before being admitted to hospital; doctors suspected of food poisoning"

b) Psychological and social reasons:

"I lost the will to live"

"I didn't feel hungry"

"I eat to survive. Eating is boring and time consuming"

"Foods taste the same; I do not bother to cook anymore"

"Food tastes different"

"I lost interest about food and I was not feeling hungry"

"I used to have a huge appetite but now I lost interest about food"

"Due to stress, family problems"

"My wife died last month"

"Because of the death of my husband"

"Due to by husband illness; I am worried and I have been carrying for him"

"Due to depression"

"I was at unemployed, at home for several months. I was worried and had a small appetite"

"The cognitive decline of my father led to a decrease in dietary intake in the last year"

"My mother's fridge is empty, with ready meals (bought by family) left all around the house. This may be explained by a cognitive decline (?)."

Appendix 4.21 - Checklist used to report standards for observational studies (STROBE, i.e. STrengthening the Reporting of OBservational studies in Epidemiology) applied to the study described in chapter 4

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on:
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title was amended – page 137
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Chapter 1; pages 138-140
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 141
Methods			
Study design	4	Present key elements of study design early in the paper	Pages 142 and 151
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 143, 145-150
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Pages 143; 148-150
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 148-151. New information about choice of confounders was added as part of these corrections in table 1.4. I have also added a figure that summarises the variables included for each aim (fig. 4.1 a)).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 145-150
Bias	9	Describe any efforts to address potential sources of bias	I added a sentence summarising

			these efforts in page 148. Details of these efforts can be found thoghout "methods" and "results" sections
Study size	10	Explain how the study size was arrived at	Page 153
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 152 (and further detail on page 161)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 152
		(*b*) Describe any methods used to examine subgroups and interactions	Page 153
		(*c*) Explain how missing data were addressed	Page 157, 159-160
		(*d*) If applicable, explain how loss to follow-up was addressed	N.A.
		(*e*) Describe any sensitivity analyses	Page 153: see subgroup analyses and the added paragraph (number 6)
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pages 154-156
		(b) Give reasons for non-participation at each stage	Pages 154-156
		(c) Consider use of a flow diagram	Page 156
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pages 158 and 161
		(b) Indicate number of participants with missing data for each variable of interest	Page 157
		(c) Summarise follow-up time (eg, average and total amount)	Pages 148-150, 161. There is no average time, everyone had a follow-up period of 6 months
Outcome data	15*	Report numbers of outcome events or summary measures over time	All tables under results (outcomes) report these numbers
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 162, 165, 169, 171, 184, 187. New information about choice of

			confounders was added as part of these corrections in table 1.4.
		(*b*) Report category boundaries when continuous variables were categorized	Page 161
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Subgroup analyses – page 167 Sensitivity analysis – page 173
Discussion			
Key results	18	Summarise key results with reference to study objectives	Pages 188-194
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 199-202
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 188-197
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 197-198
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 6

*Give information separately for exposed and unexposed groups.

Appendices of published abstracts – A to J

A – Gomes, F., Emery, P. W., Weekes, C. E. 2014. Abstract 63: Risk Of Malnutrition On Admission Predicts Mortality, Length Of Hospital Stay And Hospitalisation Costs At 6 Months Post Stroke. Stroke, 45:A63.
Oral communication delivered at the International Stroke Conference (San Diego, 2014)

INTRODUCTION
Malnutrition is related with poor outcomes after stroke which justifies the need for screening to identify and treat nutritionally vulnerable patients; however, no nutrition screening tool has been validated for this population.
This study aimed to establish the predictive validity of the Malnutrition Universal Screening Tool (MUST) in stroke patients, using several outcomes: mortality, cumulative length of hospital stay (LOS) and hospitalisation costs at 6 months post stroke.

METHODS
Patients were recruited from consecutive admissions at 2 hyper-acute stroke units in London and were screened for their risk of malnutrition (low, medium and high) according to MUST. Outcomes were obtained for each patient through a national database that contains details of all hospital admissions.

RESULTS
Of 543 recruited patients, 537 were screened within 72h of admission with MUST, 51% were males and 87% had an ischaemic stroke, with a mean age of 74.7years (range 22-99).
Results (see table) showed a strong positive association between risk of malnutrition and mortality rate (Chi square test, $p<0.001$), which remained significant after adjustment for possible confounders (Multivariable Cox Proportional Hazards Model, $p<0.001$). For patients who survived, there was a strong positive association between the risk of malnutrition and both LOS and hospitalisation costs (Kruskal-Wallis test, $p<0.001$ and $p=0.049$, respectively), which again remained significant after adjustment for possible confounders (univariate analysis of variance, $p<0.001$ and $p=0.001$, respectively).

CONCLUSION
Risk of malnutrition (as assessed by MUST) is an independent strong predictor of mortality, LOS and hospitalisation costs at 6 months post stroke, supporting the routine screening of stroke patients for risk of malnutrition on admission.

Mortality						
	n	Mortality rates (Chi-square test)	Univariate Cox Proportional Hazards Model		Multivariable* Cox Proportional Hazards Model	
			Hazard Ratio	95% CI	Hazard Ratio	95% CI
Malnutrition Universal Screening Tool	537	*p<0.001*	*p<0.001*		*p<0.001*	
Low risk	342	5.80%	Reference group		Reference group	
Medium risk	39	25.60%	4.89	2.29-10.45	3.77	1.71-8.31
High risk	156	41.70%	9.27	5.61-15.30	5.58	3.24-9.64
Cumulative length of hospital stay						
		n	**Median number of days**	**Min-Max**	**Kruskal-Wallis test (p-value)**	**Univariate analysis of variance** (p values)**
Malnutrition Universal Screening Tool	**Low risk**	322	14	2-173	*<0.001*	*<0.001*
	Medium risk	29	19	3-165		
	High risk	91	48	2-194		
Hospitalisation costs						
		n	**Median £**	**Min-Max**	**Kruskal-Wallis test (p-value)**	**Univariate analysis of variance** (p values)**
Malnutrition Universal Screening Tool	**Low risk**	320	**4918**	437-38245	*0.049*	*0.001*
	Medium risk	29	**6488**	1052-19596		
	High risk	91	**8717**	552-31905		

*results adjusted for the effects of age, gender, ethnicity, type of stroke, severity of stroke and stroke risk factors (hypertension, diabetes, dyslipidemia, smoking, ischaemic heart disease, heart failure, atrial fibrillation, previous transient ischaemic attack and heavy alcohol consumption)

** analysis of ranked LOS and adjusted for the potential confounders as above

B - Gomes, F., Emery, P. W., Weekes, C. E. 2014. Abstract T P142: Mortality And Stroke Recurrence In Obese Stroke Patients: The Obesity Paradox In a London-Based Population. Stroke, 45:ATP142.

Poster presented at the International Stroke Conference (San Diego, 2014)

INTRODUCTION

Several studies have shown a paradoxical association between body mass index (BMI) and mortality after stroke. However, the association between BMI, waist circumference (WC) and mortality and stroke recurrence is unclear.

This study aimed to determine the associations between BMI, WC and mortality and stroke recurrence at 6 months post stroke.

METHODS

Patients were recruited from consecutive admissions at 2 hyper-acute stroke units in London and were classified into 4 categories of BMI (underweight, normal weight, overweight and obese) and quartiles of WC. Outcomes were obtained for each patient through a national database that contains details of all hospital admissions.

Chi-square tests were used to compare mortality and stroke recurrence rates. Cox Proportional Hazards Models were used to compare mortality risk and survival curves between different BMI categories and WC quartiles.

RESULTS

Of 543 recruited patients, 51% were males and 87% had an ischaemic stroke, with a mean age of 74.7 years (range 22-99).

There were significant inverse associations between BMI and WC and risk of mortality at 6-months post-stroke (see table) ($p=0.001$ and $p=0.04$, respectively). After adjusting for possible confounders (age, ethnicity, gender, severity and type of stroke, stroke risk factors), these associations were attenuated ($p=0.06$ for BMI and $p=0.11$ for WC).

No significant differences were found in stroke recurrence rates between BMI groups (underweight 3.7%, normal weight 3.8%, overweight 4.5%, obese 2.8%; $p=0.91$) or WC quartiles (Q1 2.8%, Q2 5.1%, Q3 3.5%, Q4 3.6%; $p=0.83$).

CONCLUSION

After a stroke, being obese and having a larger waist circumference was associated with reduced mortality but did not affect the risk of a recurrent stroke.

	n	Mortality rates (Chi-square test)	Univariate Cox Proportional Hazards Model		Multivariable*Cox Proportional Hazards Model	
			Hazard ratio	95% CI	Hazard ratio	95% CI
Body Mass Index categories	543	*p=0.001*	*p=0.001*		*p=0.057*	
Underweight <18.5 Kg.m^{-2}	38	28.9%	1.18	0.62-2.28	0.82	0.41-1.65
Normal weight 18.6-25.0 Kg.m^{-2}	206	23.8%	Reference group		Reference group	
Overweight 25.1-30.0 Kg.m^{-2}	177	12.4%	0.48	0.29-0.79	0.57	0.33-0.97
Obese >30.0 Kg.m^{-2}	122	10.7%	0.40	0.22-0.74	0.46	0.24-0.88
Waist Circumference Quartiles	542	*p=0.046*	*p=0.044*		*p=0.107*	
1st quartile	143	25.2%	Reference group		Reference group	
2nd quartile	139	15.8%	0.60	0.35-1.02	0.64	0.37-1.09
3rd quartile	132	14.4%	0.54	0.31-0.94	0.59	0.33-1.06
4th quartile	128	14.1%	0.51	0.29-0.91	0.52	0.29-0.94

** Results are adjusted for the effect of age, gender, ethnicity, type of stroke, severity of stroke and stroke risk factors (hypertension, diabetes, dyslipidemia, smoking, ischaemic heart disease, heart failure, atrial fibrillation, previous transient ischaemic attack and heavy alcohol consumption)*

Appendix C - Gomes, F., Emery, P. W., Weekes, C. E. 2013. Weight loss prior to stroke is associated with increased mortality and length of hospital stay at 6 months post-stroke. International Journal of Stroke. 8(Suppl 3):39.
Poster presented at the UK Stroke Forum Conference 2013 (Harrogate, 2013)

Introduction:
Malnutrition is associated with poor outcomes post-stroke. Weight loss after stroke has been identified as a common concern that needs close observation (Jonsson et al, 2008), but the impact of weight loss before stroke on outcomes is not yet known.

Method:
Patients were recruited from consecutive admissions at 2 hyper-acute stroke units in London and screened for their risk of malnutrition using 2 nutrition screening tools. These included a question on unintentional weight loss in the previous 3-6 months.
NHS summary care records and data from the Hospital Episode Statistics were reviewed to obtain mortality and length of hospital stay (LOS) for each patient at 6 months post admission.

Results
Of 543 patients recruited, 51% were males and 87% had an ischaemic stroke, with a mean age of 74.7years (range 22–99).
20% of patients had unintentionally lost weight before stroke and this group had a significantly higher rate of mortality (Chi-square test $p<0.001$) and a significantly higher LOS (Mann-Whitney test, $p=0.004$) when compared with the group with no weight loss, even after adjustment for possible confounders (age, gender, ethnicity, type and severity of stroke).
A wide range of reasons for weight loss were identified by patients and carers and from medical notes, including disease-related, psychological and social reasons.

Conclusion:
Weight loss prior to stroke, which affects one in five patients, appears to be an important component of the relationship between malnutrition and poor clinical outcome after stroke. Routine screening of stroke patients for weight loss is recommended.

Appendix D - Gomes, F., Emery, P. W., Weekes, C. E. 2013. **Risk of malnutrition, Body Mass Index and Waist Circumference as predictors of mortality after stroke**. *Cerebrovascular Diseases*, 35(Suppl. 3):312

Introduction

Several recent studies have shown a paradoxical association between Body Mass Index (BMI) and mortality after stroke. This better survival of overweight and obese patients needs to be scrutinized.

The aim of this study is to compare the associations between BMI, waist circumference (WC), risk of malnutrition and mortality at 6 months after a stroke.

Methods

Patients were recruited from consecutive admissions at 2 hyper-acute stroke units based in London and, after assessment, they were divided into 4 categories of BMI (underweight, normal weight, overweight and obese), quartiles of WC and 3 groups of risk of malnutrition (low, medium and high, according to two nutrition screening tools).

NHS summary care records were reviewed to obtain mortality data for each patient at 6 months post admission.

Chi-square tests were used to compare mortality rates and Cox Proportional Hazards Models were used to compare mortality risk and survival curves between different BMI categories, WC quartiles and nutritional risk groups.

Results

Of 543 recruited patients, 51% were males and 87% had an ischaemic stroke, with a mean age of 74.7years (range 22–99).

As shown on table 1 (attached), there were significant inverse associations between BMI and WC and risk of mortality at 6-months post-stroke, i.e., the higher the BMI category and the WC quartile, the lower the risk of mortality ($p=0.002$ and $p=0.042$, respectively). However, after adjustment for possible confounders (age, ethnicity, gender, severity and type of stroke), the significant associations disappeared ($p=0.259$ and $p=0.197$, respectively). For both nutrition screening tools, the higher the risk of malnutrition, the higher the risk of mortality ($p<0.001$) and this association remained significant after the adjustment for possible confounders ($p<0.001$).

Conclusion

Risk of malnutrition is a better predictor of mortality at 6 months post-stroke than BMI or WC.

Table 1	Number of patients	Mortality rates (Chi-square test)	Univariate Cox Proportional Hazards Model		Multivariable* Cox Proportional Hazards Model	
			HR	95%CI	HR	95%CI
Body Mass Index categories (p values)	543	*p=0.002*	*p=0.002*		*p=0.259*	
Underweight (<18.5 kg/m^2)	38	28.9%	1.18	0.62-2.28	1.1	0.57-2.14
Normal weight (18.5-24.9 kg/m^2)	206	23.8%	Reference group		Reference group	
Overweight (25-29.9 kg/m^2)	177	14.4%	0.048	0.29-0.79	0.69	0.41-1.17
Obesity (>30 kg/m^2)	122	11.5%	0.43	0.24-0.79	0.61	0.33-1.124
Waist Circumference Quartiles (p values)	542	*p=0.042*	*p=0.042*		*p=0.197*	
1st quartile (<88cm)	146	25.3%	Reference group		Reference group	
2nd quartile (89 - 98cm)	143	16.1%	0.61	0.36-1.02	0.61	0.36-1.06
3rd quartile (99 – 108cm)	118	14.4%	0.54	0.30-0.95	0.62	0.34-1.14
4th quartile (>109cm)	135	14.1%	0.51	0.29-0.89	0.59	0.33-1.07
Guy's and St. Thomas' Nutrition Screening Tool (p values)	543	*p<0.001*	*p<0.001*		*p<0.001*	
Low risk	320	5.6%	Reference group		Reference group	
Medium risk	52	13.5%	2.5	1.05-5.99	2.07	0.86-4.97
High risk	171	41.5%	9.64	5.74-16.18	5.59	3.25-9.64
Malnutrition Universal Screening Tool (p values)	537	*p<0.001*	*p<0.001*		*p<0.001*	
Low risk	342	6.1%	Reference group		Reference group	
Medium risk	39	25.6%	4.65	2.19-9.89	3.51	1.63-7.63
High risk	156	41.7%	8.82	5.39-14.44	4.92	2.91-8.33

*adjusted for age, gender, ethnicity, type and severity of stroke

Appendix E - Aubrey, V. C., Gomes, F., Weekes, C. E. 2013. **Nutrition screening tools can predict outcomes at one month in patients who have had a stroke**. *Cerebrovascular Diseases*; 35(Suppl. 3):171.

Background Nutrition screening tools (NSTs) are routinely used to identify patients requiring further nutritional assessment and possible intervention. This study tested the predictive validity of two NSTs in acute stroke patients.

Method Patients admitted to St Thomas' Hospital with acute stroke were assessed using two NSTs; MUST (Elia, 2003) and Guy's & St Thomas' (GST) (Weekes et al 2004) if they were in hospital more than 3 days. Both tools assessed BMI, recent weight loss and dietary intake. Outcome data (mortality, discharge destination and length of hospital stay (LOS)) were collected retrospectively from hospital records at one month post stroke. The tools categorised patients into low, medium or high risk of malnutrition. Low/medium risk category was combined for comparison with the high-risk category. Statistical analyses were conducted using Fisher's Exact test and logistic regression (SPSS v18.0).

Results 158 patients were recruited; 79 (50 %) male; mean age 72.4 (SD 13.8) years; NIHSS score 10.2 (SD 6.4). Eighteen patients were excluded from the analysis; lack of discharge information (n = 14); MUST incomplete (n = 4). Using MUST there were significant relationships for mortality (p = 0.000) and LOS (p=0.033) with increased patient deaths and longer LOS in the high-risk category. No significant relationship was observed for discharge destination (p=0.09). Using GST there were significant relationships between risk category and mortality, LOS and discharge destination (Table 1). Patients in the high-risk category had poorer outcomes. For both tools the relationships remained significant after adjustment for age, gender and stroke severity (log regression, p< 0.05).

Table 1: Guys and St Thomas' NST

Risk of malnutrition	**Mortality (n=158)** (p=0.000)*		**Discharge (n= 144)** (p=0.015)*		**LOS in weeks (n=158)** (p=0.021)*	
	Dead	**Alive**	**Low care**	**High care**	**1-2**	**3-4**
Low/medium (n=91)	0 (0%)	91 (100%)	22 (25%)	67 (75%)	50 (55%)	41 (45%)
High (n=67)	12 (18%)	55 (82%)	5 (9%)	50 (91%)	25 (37%)	42 (63%)

*Fisher's Exact test

Conclusion Both MUST and GST reliably predict poor outcomes in stroke patients at one month. Research is needed to determine if nutrition interventions implemented following nutrition screening result in better outcomes in high-risk patients who have had a stroke.

Elia M (2003) BAPEN
Weekes CE et al (2004) Clinical Nutrition, 23:1104-12

Appendix F - Aubrey, V. C., Gomes, F., Weekes, C. E. 2013. **Concurrent validity of two nutrition screening tools in acute stroke patients.** *Cerebrovascular Diseases.* 35(Suppl. 3):705.

Introduction
There is a continued high prevalence and lack of recognition of malnutrition in hospitals. Nutrition screening tools (NSTs) are used to identify those at risk of malnutrition who may benefit from intervention. This study was used to assess the concurrent validity of two NSTs in stroke patients.

Method
Patients admitted to St Thomas' Hospital with acute stroke were assessed using two NSTs; MUST (Elia, 2003) and Guy's & St Thomas' (GST) (Weekes et al 2004) if they were in hospital more than 3 days. Both tools include three variables (BMI, weight loss and nil by mouth over 5 days). MUST requires calculation of % weight loss whereas the GST simply requires a record of weight loss with no requirement to calculate % change. An extra variable (decreased appetite) is included in GST. Both tools assign patients to one of three categories (low, medium or high risk of malnutrition). Agreement between the methods was tested using the Kappa statistic, a chance corrected measure of agreement where $\kappa > 0.6$ represents good agreement (Landis & Koch 1977). Statistical tests were conducted using SPSS (v 18).

Results
NSTs were completed for all subjects using GST (n = 158) and 154 (97 %) using MUST due to missing information for % weight loss. Data were analysed on 154 patients; 77 males (50%); mean age 72.3 (SD 13.9) years; BMI 25.7 (SD 6.1) kg/m^2; NIHSS score 10.2 (SD 6.4). There was complete agreement between the tools in 132 patients (85.7%) and chance corrected agreement between the tools was good ($\kappa = 0.746$, SE 0.046) (see Table 1). Although agreement between the tools was good, the GST classified more patients in the higher risk categories.

Table 1: Concurrent validity of two NSTs

		GST Low	Medium	High
	Low	72	10	2
MUST	**Medium**	4	2	4
	High	0	2	58

Conclusion
This study suggests good concurrent validity between the MUST and GST screening tools. Completion of MUST was not possible in a small proportion of cases. Agreement between these tools suggests either MUST or GST can be used to assess nutritional risk status in acute stroke patients.

Elia M (2003) BAPEN
Landis JR & Koch GG (1977) Biometrics 33: 159-74
Weekes CE et al (2004) Clinical Nutrition, 23:1104-12

Appendix G - Gomes, F., Hookway, C., Emery, P. W., Weekes, C. E. 2012. **A systematic review of the evidence for oral nutritional supplements in patients at risk of malnutrition who have had a stroke**. *Cerebrovascular Diseases*, 33(Suppl.2):1-2.

In the management of malnutrition in the elderly, oral nutritional supplements (ONS) significantly reduce mortality and complications in undernourished patients (body mass index < 20 kg/m^2 or with recent weight loss and/or reduced dietary intake) (Milne et al., 2009. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane Database of Systematic Reviews*). The aim of this systematic review was to evaluate the effect of ONS in acute stroke patients identified as malnourished or at risk of malnutrition using a validated screening procedure.

Inclusion criteria: randomised controlled trials (RCTs) comparing ONS with usual diet in adults aged $\geq$ 16 years with a confirmed diagnosis of acute stroke and identified as malnourished or at risk of malnutrition using a validated screening procedure. Outcome measures: mortality; morbidity; nutritional status; functional status; quality of life. The following databases were searched: Cochrane Library; Medline; Embase; Web of Science; CINAHL. All retrieved titles were reviewed by one author and potentially relevant studies were assessed independently by two reviewers against the inclusion criteria. Any differences were resolved by discussion and where necessary by consultation with a third reviewer. Quality review of all selected trials was conducted by two independent reviewers.

1,084 abstracts were retrieved of which no studies met all the inclusion criteria. Five RCTs met some criteria, but were excluded for one or more of the following reasons: included adequately nourished patients; nutrition risk status not assessed at baseline; included tube-fed patients; compared routine with intensive ONS.

Currently there is a lack of good quality evidence supporting the role of ONS in the management of patients at risk of malnutrition following acute stroke.

Appendix H - Gomes, F., Feeney, A., Prior, R., Weekes, C. E., Emery, P. W. 2012 **Predictive validity of a nutrition screening tool: clinical outcomes at one year.** *Age and Ageing*. 41 (suppl 1):43-43.

Introduction

A nutrition screening tool (NST) identifies patients who are at risk of malnutrition and may require intervention. The aim of this study was to establish the predictive validity of an NST (Weekes et al, Clinical Nutrition, 2004, 23:1104-12) in stroke and elderly care patients. The key clinical outcomes chosen were mortality and length of hospital stay (LOS).

Methods

We aimed to recruit all patients admitted to the stroke unit and three elderly care wards over two months. Following screening, patients were categorised as being at low, medium or high risk of malnutrition. Hospital records were reviewed retrospectively to establish cumulative LOS and mortality at one year after admission.

Results

Of 208 patients who were admitted, 182 (88%) were screened; mean age was 75 years (range 25 – 106).

NST risk category	**Mortality at 1 year (n=182)** *Chi-square test p<0.001)*		**LOS at 1 year (n=138)** *Kruskal-Wallis test (p=0.253)*	
	Alive	**Dead**	**Median (days)**	**Range**
low risk (50%, n=91)	79 (87%)	12 (13%)	17	1-196
medium risk (18%, n=33)	27 (82%)	6 (18%)	23	2-132
high risk (32%, n=58)	32 (55%)	26 (45%)	28	5-73

There was a statistically significant difference in mortality rate between NST risk categories, with more deaths in the high risk patients (45%). This association remained significant ($p<0.001$) after adjustment for the effects of age and sex (logistic regression).
LOS at one year for those who survived was not significantly different between groups although LOS in the high risk group tended to be longer. Age had a significant effect on the ranked LOS ($p<0.001$), suggesting it may be an important predictor of this outcome (univariate ANOVA).

Conclusion

This NST can be used to predict mortality but not LOS at one year in stroke and elderly care patients. Further research is needed in other populations.

Appendix I - Gomes, F., Crichton, S., Wolfe, C., Emery, P. W., Weekes, C. E. 2011. **Association between BMI and mortality after first-ever ischaemic stroke.** *Cerebrovascular Diseases*, 31(suppl 2):1–322.

Background:
The available data regarding the relationship between Body Mass Index (BMI) and mortality after stroke are still limited. We retrospectively studied the association between BMI and 1-year mortality after acute first-ever ischemic strokes.

Methods:
Records of patients who entered the South London Stroke Register (an ongoing population based stroke register recording first stroke in South London) between January 2004 and December 2008 were examined. Official records were obtained of all deaths within a year after a stroke. Kaplan Meier methods were used to estimate survival in the first year after stroke across BMI categories and survival functions were compared using log rank tests. A multivariable Cox Proportional Hazards Model was used to compare risk of mortality between different categories of BMI after adjusting for possible confounders (age, gender, ethnicity and severity of stroke).

Results:
From a total of 1178 patients, 640 (54%) had a record of BMI; of these, 482 (75.3%) patients had ischemic strokes. This group was divided into 4 categories of BMI: 6.6% were underweight (<18.5Kg/m^2), 36.9% were normal weight (18.5-24.9Kg/m^2), 32.4% were overweight (25-29.9Kg/m^2) and 24.1% were obese (≥30kg/m^2). There was a significant difference in survival rates between the 4 BMI categories (68.8% underweight, 78.7% normal, 89.1% overweight, 81% obesity (p=0.010)). In a multivariable analysis, there was a significant difference in the risk of mortality across BMI categories (p=0.022).With the normal weight category as reference group, the risk of mortality was higher for the underweight (hazard ratio, (HR) 1.380, 95%CI, 0.794-2.399) and obese categories (HR 1.333, 95%CI, 0.870-2.043) and lower for the overweight category (HR 0.468, 95%CI, 0.288-0.760).

Conclusion:
The decreased mortality rate in the overweight group is in line with previous findings (e.g. Vemmos et al, Stroke, 2011, 42, 30-36). However, this protection was not apparent in obese subjects.

Appendix J - Gomes, F., Feeney, A., Prior, R., Weekes, C. E., Emery, P. W. 2011. **Predictive validity of the Nutrition Screening Tool currently used in St. Thomas Hospital.** *Sinapse*, 11(1):106-107.

Introdução

Os indivíduos idosos e doentes no pós-AVC são particularmente susceptíveis à depleção nutricional e suas graves consequências. Uma ferramenta de rastreio do risco nutricional ajuda a identificar indivíduos desnutridos, de forma a que possam ser reencaminhados para uma avaliação nutricional e, caso necessário, intervenção nutricional. Estas ferramentas devem ser capazes de prever resultados clínicos negativos (validade preditiva) e, quando validadas, são apropriadas para determinada população ou patologia.

A ferramenta de rastreio nutricional em vigor no St Thomas Hospital (FSTH) foi previamente validada em algumas populações mas não em doente idosos hospitalizados e doentes com AVC.

Objectivo: Avaliar a validade preditiva da FSTH em doentes idosos hospitalizados e doentes com AVC.

Metodologia

208 doentes admitidos em 3 enfermarias para idosos e na unidade de AVCs do St Thomas Hospital foram incluídos no estudo. Sempre que a FSTH foi aplicada pela equipa de enfermagem, os doentes foram divididos em diferentes categorias de risco nutritional (baixo, médio ou alto) de acordo com o resultado obtido pela ferramenta. Posteriormente, os registos clínicos informatizados foram consultados para estabelecer os resultados clínicos negativos (tempo de internamento hospitalar e mortalidade) para cada um dos doentes, 1 e 6 meses depois da admissão hospitalar.

Resultados

Apenas 183 doentes (88%) foram rastreados e destes, 32% foram identificados com elevado risco nutricional.

Verificou-se uma diferença estatisticamente significativa na taxa de mortalidade entre as várias categorias de risco nutricional (teste do Qui-Quadrado, *p=0,027* ao 1º mês e *p=0,004* ao 6º mês), sendo a taxa do grupo de alto risco 4 vezes superior à taxa dos doentes com médio e baixo risco nutricional. A idade e sexo não afectaram esta relação (usando regressão logística).

Verificou-se também uma diferença estatisticamente significativa *(teste de Kruskall-Wallis, p=0.034)* no tempo de internamento um mês depois da admissão, sendo este tempo maior na categoria de alto risco nutricional (16 dias *versus* 14.5 e 12 dias nos grupos de médio e baixo risco, respectivamente). Esta relação foi atenuada depois de se ajustarem os resultados para o efeito da idade (usando a análise de variância, *p=0.128*).

Aos 6 meses manteve-se a mesma tendência de um maior tempo de internamento no grupo de alto risco nutricional, embora a diferença não seja significativa *(teste de Kruskall-Wallis, p=0.675).*

Conclusões

Os resultados sugerem que esta ferramenta de rastreio nutricional poder ser usada para prever os resultados clínicos negativos em doentes idosos hospitalizados e doentes com AVC. Contudo, é necessária mais investigação.

Compromissos

Bolsa de Doutoramento financiada pela Fundação para a Ciência e a Tecnologia (referência SFRH / BD / 65259 / 2009).